Prakash Srinivasan Timiri Shanmugam
Pugazhenthan Thangaraju
Nandakumar Palani
Thamizharasan Sampath *Editors*

Medical Device Guidelines and Regulations Handbook

Springer

Medical Device Guidelines and Regulations Handbook

Prakash Srinivasan Timiri Shanmugam
Pugazhenthan Thangaraju
Nandakumar Palani • Thamizharasan Sampath
Editors

Medical Device Guidelines and Regulations Handbook

Springer

Editors
Prakash Srinivasan Timiri Shanmugam
Global Product Safety & Toxicology
Avanos Medical, Inc.
Alpharetta, GA, USA

Nandakumar Palani
R&D Engineer, Medical Devices
Milpitas, USA

M.Sc., Electronics
Chennai, India

Pugazhenthan Thangaraju
Department of Pharmacology
All India Institute of Medical Sciences (AIIMS)
Raipur, Chhattisgarh, India

Thamizharasan Sampath
Department of Pharmacology
Maitri College of Dentistry & Research Centre
Anjora, Durg, Chhattisgarh, India

ISBN 978-3-030-91854-5 ISBN 978-3-030-91855-2 (eBook)
https://doi.org/10.1007/978-3-030-91855-2

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

ISO 14155: Clinical Investigation of Medical Devices for Human Subjects

Karnika Singh

1 Introduction

The international standard ISO 14155 was formulated by Technical Committee ISO/TC 194, Biological evaluation of medical devices, to define good clinical practice during clinical investigation of medical devices in human subjects. This includes the design, conduct, recording, and reporting of clinical investigations as well as the safety or performance of medical devices for regulatory purposes. It consists of two parts, ISO 14155-1, which specifies procedures for the "conduct and performance," and ISO 14155-2 that contains *prerequisites for the "preparation of Clinical Investigation Plans (CIPs)"* for the clinical investigation of medical devices. First version of ISO 14155 was released in 2003 (ISO 14155:2003); since then it has been modified several times, and the latest version came out in 2011 and is the standing version till date known as the ISO 14155:2011. It should be noted that ISO 14155 is not applicable to in vitro diagnostic medical devices. In this chapter, we will be discussing both parts of this ISO.

2 Structure of ISO 14155:2011

The ISO 14155:2011 is divided into several sections, namely:

1. Scope
2. Normative references (ISO 14971:2007)
3. Terms and definitions
4. Ethical considerations

K. Singh (✉)
The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_1

5. Clinical investigation planning
6. Clinical investigation conduct
7. Suspension, termination, and closeout of the clinical investigation
8. Responsibilities of the sponsor
9. Responsibilities of the principal investigator

The original document also has several annexes associated with clinical investigation plan (CIP), investigator's brochure (IB), case report form (CRF), clinical investigation report, essential clinical investigation documents, and adverse event categorization.

In this chapter each part of ISO 14155:2011 will be discussed in the light of above sections.

3 ISO 14155-1

3.1 Scope

As mentioned above, this part of ISO 14155 defines the "general requirements for biological tests" aimed at protecting human subjects, assuring that clinical investigation is carried out with optimal scientific conduct and helps the sponsors, monitors, investigators, ethics committees, and regulatory authorities and bodies involved in the conformity assessment of medical devices to oversee the compliance of the standard. It specifies the requirements to plan a clinical investigation with regards to the concerned medical device's performance in terms of mimicking clinical use, adverse events that might occur during normal conditions of usage, evaluation of acceptable risks associated with the assigned performance of the medical device and organization, conduct, monitoring, data collection, and documentation of the clinical investigation of a medical device. All these requirements are applicable to clinical investigations pertaining to human subjects.

3.2 Terms and Definitions

Adverse device effect: As the name suggests, it means any unexpected response to a medical device. This could be any event as a consequence of defects or faults in the "instructions for use" and/or arrangement of the device or simply user error.

Adverse event: This refers to the development of any unfortunate medical condition in a subject. However it should be kept in mind that there may not be a direct association between the adverse event and the medical device.

Case report form: Form designed to catalog all the information notified to the sponsor about each human subject as needed by the clinical investigation plan.

Clinical investigation: A study intended for analyzing the safety and performance of a particular device in humans.

Clinical investigation plan: Often referred to as protocol, this document describes all the information regarding the "rationale, objectives, design and proposed analysis, methodology, monitoring, conduct, and record keeping of the clinical investigation."

Clinical investigator: Person or institution that is conducting the clinical investigation and would be liable for the good health of the human subjects that are part of the clinical study.

Clinical investigator's brochure: A collection of clinical and nonclinical information about the device under investigation relevant to the human subjects of the study.

Clinical performance: Performance or action of a medical device when used with correct intent on suitable human subjects.

Coordinating clinical investigator: It is the person (usually appointed by the sponsor) who coordinates the work of a multicenter investigation.

Ethics committee: An independent panel created for ensuring the safety, well-being, and human rights of the subjects participating in the clinical study.

Final report: Document containing the details, results, and interpretation of the conducted clinical investigation.

Informed consent: A legal document confirming a subject's voluntary participation in a clinical study after he/she has been informed about all aspects of the clinical investigation pertaining to their decision to participate.

Investigation center/investigation site: Site or institution of clinical investigation.

Medical device: A contraption along with the software required for its operation used for various diagnostic purposes like prevention, monitoring, treatment, or alleviation of disease; rectification of an injury or handicap; alteration of anatomy or physiology of a biological process; conception control; etc. Such a device is not supposed to function in the human body by any pharmacological, immunological, or metabolic ways. However, any such outside assistance can be taken to improve its function.

Monitor: Person recruited by the sponsor for assessing the compliance of investigator with the clinical investigator plan, performance of source data verification, and regular progress reporting to the sponsor.

Multicenter investigation: A clinical investigation that occurs at two or more sites according to original clinical investigation plan.

Principal clinical investigator: A clinical investigator responsible for arranging clinical investigation at a single site.

Serious adverse device effect: An adverse device effect resulting in a serious adverse event or any series of events in which intervention was not possible due to various reasons.

Serious adverse event: An adverse event leading to death or severe decline of health of the human subject. This includes any life-threatening illness or injury, lasting impairment of a body part, hospitalization, surgery, etc. Congenital anomalies and fetal morbidity also fall under this category.

Source data: Original information in the records collected during the clinical investigation comprising clinical findings, observations, etc. that may be used to reconstruct or evaluate the initial clinical investigation.

Source documents: Original data, documents, and records, for example, laboratory notes, hospital records, pharmacy records, photographs, radiographs, etc.

Sponsor: Also known as promoter, it is the person responsible for proper institution and/or implementation of a clinical investigation. The clinical investigator can also carry out this role.

Subject: Human being who participates in a clinical investigation either as a receiver of the test device or as a control.

3.3 Ethical Considerations

Declaration of Helsinki (DoH)

It was created by the World Medical Association (WMA) in 1964 as a policy statement for ensuring the ethical treatment of human subjects in clinical investigation. Since then this document has been amended seven times and the latest accepted version was formulated in 2013. However it should be noted that this is not a legal document, even though it is referred to at every step of a clinical investigation. The DoH highlights the fundamentals like basic respect of the individual, their right to informed decisions, their welfare, that the clinical investigation should be carried out after detailed scientific investigation, and, above all, ethical considerations.

Improper Influence or Inducement

The participants of the study (subjects, officials, and other parties) should not to be improperly influenced or induced by any means during the clinical investigation.

Compensation and Additional Health Care

This includes all the provisions decided for the compensation of subjects due to any injury while participating in the clinical investigation. This also comprises additional healthcare provisions that would be employed during an adverse device effect. All these occurrences if happen shall be documented.

Responsibilities

It is the responsibility of the participating parties to ensure that clinical investigation is conducted ethically, especially as far as their role is concerned.

3.4 General Requirements

Formal Agreement

This is a written and signed agreement between the sponsor, the clinical investigator(s), and other involved parties that describe their responsibilities.

Qualifications

This entails to the required educational qualification and experience of the personnel involved in the clinical investigation.

Clinical Investigation Plan

This is discussed more in part 2.

Design of the Clinical Investigation

The design of clinical investigation should center around testing the suitability of the device for the intended medical purpose such that the results obtained shall be authentic, supportive, and relevant to the investigation's objective.

Confidentiality

This requires the safekeeping of patient data such as their name and identifying information. For this, the case reports form should not use such information; the patient data should be secured under unauthorized access and should be limited to only reports and scientific publications.

Start of Clinical Investigation

The following things should be kept in mind before starting a clinical investigation:

1. A written and signed clinical investigation plan
2. Approval of the ethics committee
3. Regulatory clearance

Informed Consent

It is mandatory to obtain and document the informed consent in writing from every subject who decides to enroll in the clinical study. It is structured in two parts: study information and signature area. They can be together in one document or two separate documents.

ISO 14155-1 details the "process of obtaining informed consent." It should not involve any pressurizing or influencing of subjects to participate. Subject's legal rights should not be waived. Nontechnical language should be used in the consent form such that the subject or his/her legal representative easily understands it. The subject should be given ample time to consider their participation in the study. The informed consent should be signed and dated by the subject or his/her legal representative and the clinical investigator. It should be outlined how the informed consent would be obtained for cases when the subject is unable to give it. Some circumstances could be when the subject is a fetus, child, juvenile, seriously ill, unconscious, or mentally incapable to do so. In such conditions, a legal guardian or representative is authorized to give informed consent. All this has to be documented in the clinical investigation plan.

Informed consent is a really important part of a clinical investigation; therefore the subject needs to be properly informed of certain things before obtaining their informed consent. First, is the description and purpose of the study detailing the involvement of research, investigation's objective, duration of the study, how the subject would be involved in the study, specifics about the medical device that is being investigated, and explanation of the procedure with an emphasis on the experimental part. Second, is the mentioning of any foreseeable risks that accompany the investigation along with any side effects. The consent should also describe the potential benefits, the subject or others might have if the study is a success (have a positive outcome). It should also include the alternative therapies that are available to the current medical condition/device. The consent should clearly state that the subject's participation would be kept confidential; his/her medical details would only be accessible to the regulatory authorities or sponsor's delegates; and the results of the study may be published but the subject's identity would not be revealed. The consent should also state that the subject is liable to get compensation if he/she is injured during the study and additional healthcare needs to be administered because of an adverse device effect. The compensation can be financial and the details of that should be outlined. The contact person needs to be clearly defined in the consent to which the subject can ask questions about the study in general, inform about an injury, etc. The conditions of termination of participation by the investigator should also be included in the consent. Finally, it should state that any new findings related to the subject's participation would be made available to them.

The signing of informed consent agreement means that the participating individual or his/her legal representative would participate and comply with the clinical investigation; they would inform their personal physician of their participation in the study or their disagreement for this information release and that they would allow the use of any personal data relevant to the study in the clinical investigation.

In the event of an early termination of the study, it is the sponsor's responsibility to promptly inform the clinical investigators and investigation centers of the termination along with the reason of termination. The ethics committee should also be informed of the termination and its reason either by the sponsor or the investigator or the investigation center. In some instances the subjects' physicians may also have to be informed.

Document and data control are critical aspects of a clinical investigation. It is important to safeguard subject's privacy as much as possible. A case report form should be maintained for each patient which would record their data as required by the clinical investigation plan. Similarly, all subjects enrolled currently or previously in the study shall be accounted for and documented. All the data obtained in the study has to be kept confidential and only the clinical investigator would have access to it. Monitor would only have access to source documents and other information necessary to ensure investigator compliance with the study plan, rules, and regulations and judge the progress of clinical investigation. The clinical investigator should allow auditing of their clinical investigator procedures.

Documentation

Clinical investigator's brochure and other documents like clinical investigation plan, case report forms, etc. should be prepared before the start of clinical study. The clinical investigator brochure should contain a summary of literature, clinical investigation design, and rationale for the planned use of the medical device. The description of the device should be included according to ISO 14155-2. The mechanism of action of the device should be described along with the supporting scientific literature. The manufacturer's instructions for use and installation and possible side effects and contraindications should also be included if required. The expected clinical performance of the device and materials used to manufacture the device should be outlined. The experimental results pertaining to the device including biological, clinical, and preclinical studies should be reported. Any previous reports regarding the device or any similar device should also be mentioned. A compiled list of international standards and results of the risk analysis should also be included. The clinical investigator brochure should be regularly updated with any piece of significant information along the course of clinical investigation and shall be conveyed to the clinical investigators.

Other documents that should be prepared in advance, include the clinical investigation plan; the curriculum vitae that is current, signed, and dated; the institution(s) where the clinical study would happen; written approval of the ethics committee and related documents; all communication with authorities as needed by national legislation; agreement between the principal investigator and the sponsor; insurance certificates; informed consent forms and other materials provided to the subjects; case report forms; reporting forms for adverse events and adverse device effects; and contact information of the monitor.

Sponsor

It is the responsibility of the sponsor to design and communicate all the duties and functions relating to the clinical study. They will ensure documentation showing that, investigator, sponsor, and monitor comply with ISO 14155, the clinical investigation plan and subsequent amendments, and applicable regulatory requirements through a transparent system. The responsibilities of a sponsor have been listed in detail in the ISO 14155 document.

- Selection of investigator and the investigation center for the study and coordination of the clinical investigator if required.
- Selection and appointment of monitor for the study or acting as monitor themselves. The sponsor is supposed to perform this duty along with the monitor and clearly outline the guidelines for taking care of noncompliances and missing data.
- Assemble and update the clinical investigation brochure.
- Supply the clinical investigator with clinical investigation plan, approved amendments, and the clinical investigator's brochure.
- Sign the approved clinical investigation plan.
- Provide the devices that are to be studied in the clinical investigation.
- Make sure that the clinical investigator has the appropriate information and/or training in the use of device as per the clinical investigation plan.
- Assure that all the deviations from the original clinical investigation plan have been reviewed with the respective clinical investigator(s) and recorded in the case report form and the final report of the clinical investigation.
- Report and review the adverse events and adverse device effects with the clinical investigator to the ethics committee, safety monitoring committee, and any other relevant authorities.
- Report in writing to all clinical investigators involved in the study, the serious adverse effects reported to them during the investigation. The report shall be sent based on the perceived risk.
- Immediately inform the clinical investigator if the study has been prematurely terminated or suspended along with the concerned regulatory authorities. Also explain the reason of premature termination or suspension.
- Tell the clinical investigator(s) about the developmental status of the device, and state the requirements essential to verify the performance of the device.
- Review and approve any departure from the original study plan, and perform any relevant corrective or preventive actions.
- Collect, secure, store, and ensure completion by involved authorities of the listed documents:
  - All the documents listed in the "documents" section
  - Case report forms, signed and dated
  - Records of any adverse events and adverse device effects reported to the sponsor during the clinical investigation
  - Final report of the clinical investigation

- Make sure that device is accountable and traceable.

Monitor

The monitor is responsible for the following:

- Verifying compliance with the clinical investigation plan is maintained and any departure from the clinical investigation plan is reviewed and documented with the clinical investigator and at the same time reported to the sponsor.
- Verifying that the device is being used in accordance with the clinical investigation plan and reporting to the sponsor if any modifications are needed for the device or its methodology.
- Monitor that the clinical investigator(s) currently have the staff and facilities to conduct the clinical study safely and effectively.
- Verify that the clinical investigators have continued access to adequate number of subjects and clinical devices.
- Check that all consent forms obtained from the subjects at the time of enrollment are signed and dated before any study-related procedures are started.
- See if the case report forms are complete and timed, and match the source of the data.
- Ensure that adverse events and adverse device effects are recorded and reported to the sponsor, followed according to respective procedure.
- Device accountability and traceability procedures are in place and are maintained.
- The equipment under study is calibrated regularly and documented at the same time.
- There is documentation of subject withdrawal and noncompliance, regular discussion with clinical investigator, and report to the sponsor.
- Review the noncompliant findings or required modifications with the clinical investigator, and write a monitoring report to the sponsor disclosing the above information.

Clinical Investigator

The clinical investigator is an appropriately qualified clinician with a license to practice medicine. He should have enough experience in the field and also training for the device usage under investigation. He should be thorough with the background and requirements of the methods to be followed in the clinical study. The clinical investigator should be well versed in the art of obtaining informed consent.

Like the sponsor and the monitor, the clinical investigator also has several responsibilities to ensure the smooth day-to-day conduct of the clinical study and safety of the human subjects involved in the study.

- The clinical investigator should have all the resources to properly conduct the clinical study.

- He/she should also make sure that there is no conflict of interest because of the study.
- The clinical investigator should regularly obtain important information from the sponsor concerning the device under investigation.
- He/she should also completely go through the clinical investigation plan before signing it.
- He/she should help the monitor and the auditor to rectify case report forms for any inconsistencies or missing information. Also this would give the investigator a chance to verify compliance of the two officials with the clinical investigation plan and perform source data verification as well.
- They should discuss the possibilities of modification to the clinical investigation plan with the sponsor and the monitor and obtain sponsor's written approval.
- They are also responsible for making sure that the clinical investigation plan is followed by all those involved in the study and that any departure from the plan is documented and reported to the sponsor.
- The clinical investigator has to make the necessary arrangements for the proper conduct and completion of the clinical study.
- They also have to make sure that necessary measures are in place for emergency treatment to protect the subjects in the study.
- Obtaining appropriate ethics committee approval is also the responsibility of the sponsor in order to start the clinical study at the respective center.
- Give the results from the ethics committee to the sponsor.
- Communicate to the ethics committee about any significant changes that have been made to the study plan as approved by the sponsor along with the appropriate reasons.
- Notify the ethics committee of any adverse side effects.
- Also notify the sponsor of all adverse events and adverse device effects as they happen.
- Make sure that the subjects are recruited in an adequate manner.
- To establish that the recruited subjects were given adequate information to provide informed consent.
- Assure that informed consent is obtained and recorded.
- Ensure that clinical records clearly indicate that enrollment of subjects in respective study; if needed, the subjects shall be provided with a means to prove their association with the study along with identification and other compliance documents. The subject's physician may also be involved if required.
- Like the sponsor the clinical investigator also has to ensure that the subjects are briefed with procedures to follow during an emergency situation. Under such conditions the prior approval of sponsor shall not be required, and this would not be considered a breach of agreement. However, these deviations would be documented and reported to the sponsor.
- Any information that is made public as a part of the clinical investigation about the subjects and is required for clinical study's continuation shall be conveyed to the sponsor and if appropriate to the subject's physician as well.

- The clinical investigator is also responsible for informing the subjects and their physician about any premature termination or suspension of the clinical study along with the reason of termination.
- The clinical investigator is responsible for accuracy, legibility, and security of all data collected during the study, documents, and patient records at the investigation site both during and after clinical investigation. The clinical investigator should sign the case report forms. Data shall be altered, initiated, and dated only by the authorized personnel, and original data has to be retained for comparison purposes.
- Make sure that the basic data collected during the study are retained for the minimum time specified in the plan.
- The clinical investigator shall also be responsible for the supervision and assignment of duties to the responsible personnel at the clinical investigation center involved.
- Account all the devices that are part of the investigation.

The quantity of the devices received for the study should be adjusted with the number of devices used, discarded, or returned.

Final Report

A final report of the clinical study has to be completed even when the study is prematurely terminated. It has to be in a written format and signed by the sponsor and the coordinating investigator, principal clinical investigator(s) from each center. This document would be made available upon request to all clinical investigators and the ethics committee. The final report should comprise a detailed identification of the device(s), description of the methodology and design of the study, any departures from the study plan, data analysis with the statistics, and a critical assessment of the aims of the study. The final report will include data from all the centers and enrolled subjects. The subjects shall not be identifiable from any part of the report or the published data. All clinical investigators would review the report and comment on it. The sponsor will keep the record that all clinical investigators have been given the final report for review and comments. If any investigator disagrees with any part of the final report, his/her comments shall be recorded and conveyed to other investigators. If the coordinating investigator or other investigator is unable to or refuses to sign the report, a justification shall be given for the not signing of the final report.

4 ISO 14155-2

4.1 Scope

This part of ISO standard details the requirements for laying out the CIP for the clinical investigation of medical devices. A CIP compiled in accordance with this ISO helps in establishing the validity and reproducibility of the results of a clinical study.

4.2 Terms and Definitions

End point – primary: Principal indicator measured or set to evaluate the primary objective of a clinical study

End point – secondary: Indicator measured or set in addition to the primary end point to determine some other aim of the study

Point of enrollment: The time at which, after recruitment, the subject signs the informed consent forms and officially becomes the part of the study population

Follow-up period: The period of the clinical study where the effects of the medical device under investigation are observed in the enrolled subjects

Recruitment: The process of classifying subjects who may be appropriate for the clinical study under consideration

4.3 Requirements

All requirements for this part of ISO are same as ISO 14155-1.

4.4 Clinical Investigation Plan (CIP)

The sponsor and the clinical investigator(s) would prepare this document such that it would be used for optimizing the scientific validity and reproducibility of the results. All this would be done in accordance with current clinical standards relevant to completing the aims of the study. The CIP would have information in the organized clauses. The other documents like clinical investigator's brochure, sponsors standard operating procedures, etc. should be referenced in the CIP and provided on request. The sponsor can decide that any of the following requirements is not applicable in a particular situation; he/she would have to provide a clear statement explaining the omission of information in each situation.

4.5 General Information

Identification of the Clinical Investigation Plan

The CIP and any of its amended versions would be identified by the title of the study and its reference number. It will also include the version/issue number and the date to trace it back to the signatories. Each page would contain the version number.

Clinical Investigators, Principal Clinical Investigator, Coordinating Clinical Investigator, Investigation Center/Site(s)

The CIP would list the contact details (name, address, and professional position) of the clinical investigator(s), principal investigator(s), and the coordinating clinical investigator if applicable. Similarly, name and address would be provided for the institutions at which the study would take place. The name and address of additional centers or persons involved in the study in terms of patient management, testing, or analysis would also be included.

Sponsor

The contact details of sponsor of the study would be included in the CIP whether they are in state or a foreign country.

Monitoring Arrangements

The monitoring arrangements would be outlined in the CIP and the planned extent of the source data verification.

Data and Quality Management

The CIP would define the protocol for database management, treatment of data, source data verification, data archiving, retention period, and other quality control processes.

An Overall Synopsis of the Clinical Investigation

The CIP would give a summary or outline of the clinical investigation. It can be accompanied with graphics like flowcharts showing the key stages of the study or other important information relevant to the study.

Approval and Agreement to the Clinical Investigation Plan

The sponsor, coordinating investigator, and the principal clinical investigator(s) in each center shall comply with the CIP and its amendments and express their approval and consensus by signing and dating an appropriate document.

4.6 Identification and Description of the Medical Device to Be Investigated

The CIP would include or reference to a brief description of the device under investigation and its designated purpose. The subsequent information shall be provided:

- The device manufacturer, its model, or type number along with software version and accessories to allow full identification and traceability. If this information is unknown at the time of CIP preparation, a method of traceability would be laid down for before and after the study.
- The designated purpose of the device as declared by the manufacturer including the contraindications and clinical implications in the study and the target populations.
- Characterization of the device including any components that would come in contact with tissues or body fluids. This would consist of the details of any medicinal products, human and/or animal tissues or their derivatives, or other biologically active substances.
- Instructions for installation and use of the device along with any necessary storage and handling requirements, arrangement for use and reuse and any checking before safety and performance, and any precautions required after use.
- A review of required training and experience needed for the use of device under study.
- A statement of involved medical or surgical procedures in the use of the said device.

4.7 Preliminary Investigations and Justification of the Study

Literature Review

The CIP shall contain relevant scientific literature and/or unpublished data and reports along with a list of references that have been reviewed. The purpose of this review is to justify the proposed study design. The review would pertain to the intended purpose of device under investigation and prospective method of use.

Preclinical Testing

The review would recap the preclinical testing that has been done for the device under investigation to support its use in human subjects, along with an analysis of the results from such testing. This would include the results of the preclinical testing, design calculations, in vitro tests, mechanical and electrical testing, reliability checks, and software validation relating to the function of the device. Other results from performance tests, ex vivo testing, biological testing and/or safety tests in animals, justification of tests done, and timeline of such results would also be included.

Previous Clinical Experience

The CIP would also include the results from the previous clinical investigations, if any and clinical use that is pertinent to the current study. The CIP would also talk about any previous data that is out there regarding device usage or similar devices that are currently in use. All this comprises an evaluation of adverse device effects and any past experiences of modification or recall.

Device Risk Analysis and Risk Assessment

The CIP shall provide results of a risk analysis and assessment. This would weigh the balance between anticipated clinical benefit and the risks connected with the device and its method of use as stated by the risk management. Probable interactions with competent medical interventions shall be tabulated, along with a statement of the expected clinical benefit. This would comprise an evaluation of adverse device effects and any prior report of modification or recall in association with safety and clinical performance of the device under study and similar devices.

Objectives of the Clinical Investigation

The CIP would clearly state the hypothesis and objectives, both primary and secondary, of the clinical study and populations on which the device would be tested. These would specifically include:

- Predictions and suspected performance of the devices that are to be tested
- Risks and predictable adverse side effects that are to be evaluated
- Specific hypotheses to be tested by statistical data obtained from the study

Design of the Clinical Investigation

The scientific credibility of a clinical study lays on its design; therefore the CIP shall supply the following information:

- Explanation of the type of investigation to be conducted (e.g., comparative double-blind, parallel design, with or without a control group) with appropriate rationale for the choice
- Review of the controls
- Methods employed to reduce bias
- Primary and secondary end points with reason for this choice
- The variables to be tested with relevant reason to achieve the end points
- The methods and timing for checking, documenting, and evaluating variables
- Assess the equipment to be used for analysis of study variables and the setup for monitoring the sustenance and calibration
- Inclusion criteria for subject election
- Exclusion criteria for subject election
- Point of enrollment
- Detailed description of the protocol that the subjects would be subjected to during the study along with a record of other devices or medication to be utilized during the usage of the device under investigation or during the follow-up course
- Criteria and methods for withdrawal and discontinuation of subjects from the study and their accountability, along with the follow-up procedures of these subjects, if feasible
- Number of subjects needed for the study, time required to recruit this number, total devices needed for the study, and explanation for all these numbers. For multicenter studies, the minimum number of subjects to be involved from each center has to be specified and justified. If there is a chance of the validity of the study results to get affected, the number of subjects enrolled at each center would be taken into consideration.
- Strategy for documenting and evaluating adverse events, adverse side effects, and/or outcomes
- Time of use of the device or its control and its follow-up time in a specific subject of the study along with the justification
- Any known or expected factors that may impact results or their interpretation, for example, subject baseline characteristics, concomitant medication, use of other devices or subject-related factors (age, gender or lifestyle), etc. The means (subject selection, study design-stratified randomization, statistical analysis) of addressing these variables in the study have to be outlined.

Statistical Considerations

The CIP will contain a description and explanation of hypothesis and statistical design, method, and the analytical procedures to be employed. This encompasses:

- Reasoning for the sample size, significance test to be used, power of the study, and predicted dropout rates, along with the justification of all these choices
- Pass/fail criteria to be used on the results of the study
- Plan for an interim analysis, where required, and the criteria for the cessation of the study on the statistical grounds
- Protocols for reporting any departure(s) from the original statistical plan. All this would be recorded in the CIP or final report.
- Criteria for choosing the subjects to be included in the study with the explanation
- Protocols for accounting of data, handling of missing, unused, or false data, drop-outs, and withdrawals along with the explanation of leaving out particular information from hypothesis testing

Deviations from the Clinical Investigation Plan

All the deviations from the CIP would be recorded with a justification. These deviations would be communicated to the sponsor, who will analyze and evaluate its significance. The reasons for retraction and suspension of any subject from the study would be documented. The ethics committee or other regulatory authorities can be involved if needed. If the reasons involve safety and lack of effectiveness, that subject would still be followed up in the study, if feasible.

Amendments to the Clinical Investigation Plan

Any modifications to CIP shall be done only after agreement between sponsor and the clinical investigator(s). These modifications would be recorded with required explanations. If the list of clinical investigators and centers is changed, the list will not be formally updated, and only sponsor would maintain the updated list and make it available on request. The final list of all centers and investigators shall be included in the final report.

Adverse Events and Adverse Device Effects

The CIP would contain:

- Emergency contact information for reporting of serious adverse events and serious adverse device effects
- Specifics of predictable adverse events and adverse device effects (e.g., serious/nonserious, device-related/non-device-related, their probable incidence, methods for their management)
- Detailed procedures for reporting all adverse events and adverse device effects to the sponsor, ethics committee, and other regulatory authorities in agreement with

relevant regulations, specifications of those types of events, device-related and non-device-related that would be documented along with its timing

Early Termination and Suspension of the Investigation

The CIP would lay down the criteria and provisions for early termination or suspension of the study. This can apply to the whole study or one or more centers. If the study includes blinding techniques, the rules to access and break the code have to be described. The CIP would define the subject follow-up requirements to be considered after an early termination or suspension of the study, wherever relevant.

Publication Policy

Although all the data collected in the study should be put up for publication, still the CIP shall state whether the results from the study would be submitted for publication or not. It would also specify the extent and the conditions under which the results obtained from the clinical study would be proposed for publication.

Case Report Forms (CRF)

In CRF, all the information is listed that needs to be recorded during a study. The CRF shall mirror the contents of the CIP and clearly show its version number. Any amendments to the CRF would also contain a version number, and each page would be marked by the study number and identification of the subjects, whose data are present in the CRF. If the necessity of amending the CRF arises, the sponsor shall determine whether the amendment is necessary or not by reviewing the CIP.

References

1. ISO 14155:2011 Clinical investigation of medical devices for human subjects—Part 1: General requirements
2. ISO 14155:2011 Clinical investigation of medical devices for human subjects—Part 2: Clinical investigation plans

ISO 13485: Medical Devices – Quality Management Systems, Requirements for Regulatory Purposes

B. Karthika and A. R. Vijayakumar

Introduction

The International Organization for Standardization (ISO) develops standards for use worldwide, and it is a national standards body for worldwide federation. The effort of setting goals for international standards is carried out through ISO technical committees, and also international, governmental, and nongovernmental organizations are in association with ISO to frame this. In electrotechnical standardization, ISO collaborates with the International Electrotechnical Commission (IEC). ISO 13485 guides companies to do their share in protecting medical devices' consumers and users. ISO 13485 frames criteria for the best quality management system (QMS) in international standard that specifies requirements for a QMS for organization involved in all stages of the medical device, including design and development, production, storage, distribution, installation, servicing, final decommissioning, disposal of medical devices, and provision of associated activities (e.g., technical support). This international standard requirement can also be used by suppliers or other external parties providing product (e.g., raw materials, components, subassemblies, medical devices, sterilization services, calibration services, distribution services, maintenance services) to conform with such organizations to maintain the standard.

International Standard Process Approach

This international standard process approach is for quality management. A process, it could be of any activity that receives input and converts it to output. The output from one process mostly directly forms the input to the next process. For an organization to function efficiently, it performs to identify and manage numerous linked processes. The application for a system of processes in an organization is for the identification and interactions of these processes with their management to produce the desired outcome referred to as the "process approach." The quality management system of process approach emphasizes:

B. Karthika (✉)
Department of Oral Medicine and Radiology, Priyadarshini Dental College and Hospital, Pandur, Tamil Nadu, India

A. R. Vijayakumar
Department of Pharmacology, JIPMER, Karaikal, Puducherry, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_2

- The understanding and meeting requirements
- The consideration of processes in terms of added value
- In obtaining results of process performance and effectiveness
- In improving processes based on objective measurement

Clarification of Concepts

ISO 13485 international standard is qualified by the phrase "as appropriate" for the product to meet requirements; compliance with applicable regulatory requirements; the organization to carry out corrective action; and the organization to manage risks. When the term "risk" is used, the application of the term within the scope of this international standard pertains to safety or performance requirements of the medical device or meeting applicable regulatory requirements. When a need is required to be "documented," it is also essential to be established, implemented, and maintained. When the term "product" is used, it also means "service." Product is for the output that is intended for, or required by, a customer, or any intended output resulting from a product realization process. Regulatory requirements are to encompass requirements contained in any law applicable to the user of this international standard (e.g., statutes, regulations, ordinances, or directives), for the quality management system and for the safety or performance of the medical device. In this international standard, the verbal forms and their indication are as follows: "shall" indicates a requirement; "should" indicates a recommendation; "may" indicates permission; "can" indicates a possibility or a capability; information marked as "NOTE" is for guidance in understanding or clarifying the associated requirement.

Quality Management System (QMS)

QMS criteria are superior business practices to set quality goals, to ensure regulations and all requirements are understood and met, to train the employees, to control the production processes, to purchase from the suppliers that can provide products that meet requirements, and to correct the problems to make sure that they do not happen again.

Once the QMS is established with all the criteria, a registrar is contracted to conduct an audit, and the company will be ISO 13485 registered. ISO 13485-registered companies can market and advertise their registration certificate. So the existing and potential customers will know that you have a good QMS for your medical devices. ISO 13485 international standard that describes QMS requirements for medical devices contains five clauses that are numbered as 4, 5, 6, 7, and 8.

- Clause 4 for quality management system
- Clause 5 for management responsibility
- Clause 6 for resource management
- Clause 7 for product/service realization
- Clause 8 for measurement, analysis, and improvement (Fig. 1)

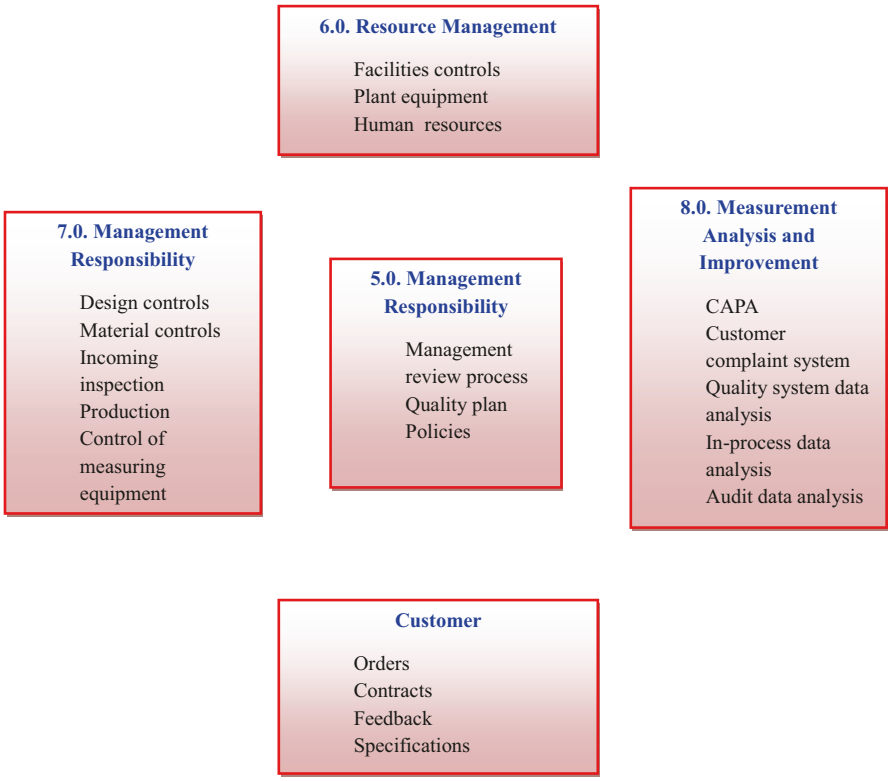


Fig. 1 ISO 13485 model system. (Courtesy: David N. Muchemu. Designing a world-class quality management system for FDA regulated industries: Quality system requirements (QSR) for cGMP. Author House Publisher, Bloomington, Indiana; 2008: Page: 43)

ISO 13485 Standard

This standard can be used by an organization involved in all stages of the life cycle of a medical device and by suppliers and other external parties providing product to such organizations.

1. **Scope of the Standard**

- Is about the standard and how it applies to organizations.
- The requirements in this standard can be used by suppliers and other external parties providing products.
- Exclusions of requirements in clause 6, 7, or 8 in the QMS depending on organizations' role.

1.1. International Standard Used by Suppliers or External Parties That Provide Product Including QMS-Related Services to Such Organizations

1.2. The Requirement of Clause 6, 7, or 8 Can Be Not Applicable to the Organization with Documented Justification

- "Risk" – pertains to safety and performance requirements, or meeting regulatory requirements
- "Documented" – to be established, implemented, and maintained
- "Product" – now means the product or for service. The output that is intended for a customer, or for an intended output of product realization
- "Regulatory requirements" – are the legal requirements for the quality management system and for the safety or performance of the device

This international standard process is applicable to the organization, but not performed by the organization; they are the responsibility of the organization and are accounted for the organization's quality management system by monitoring, maintaining, and controlling the process.

2. **Normative Reference of the Standard**

References from another document used along with the standard; updated to ISO 9000:2015

3. **Terms and Definitions of the Standard**

It gives definitions that are related to medical devices:

- Removed: refers to supply chain explanation, active implantable medical device, and active medical device
- Modified: refers to complaint, labeling, implantable or active, or sterile medical device
- Added: refers to authorized representative, clinical evaluation, distributor, and importer, life cycle manufacturer, medical device family, performance evaluation, post-market surveillance, product (from 9000:2005), purchased product, risk, risk management, sterile barrier system, and sterile medical device

4. **Quality Management System (Fig. 2)**

4.1. ***The General Requirement***

The entire clauses are reorganized:

- Document QMS and maintain its effectiveness.
- Document the role taken by the organization.
- Establishment based on risk approach to control the processes.
- Requirements validation of application of computer software.

4.2. ***Documentation Requirements***

Re-organized paragraphs:

4.2.1. The Quality Manual
4.2.2. The Medical Device File (New Subclause)
4.2.3. To Have Control of Documents
4.2.4. To Have Control of Record – Confidential Health Information
4.2.5. Security of Documents/Records – Prevention of Loss

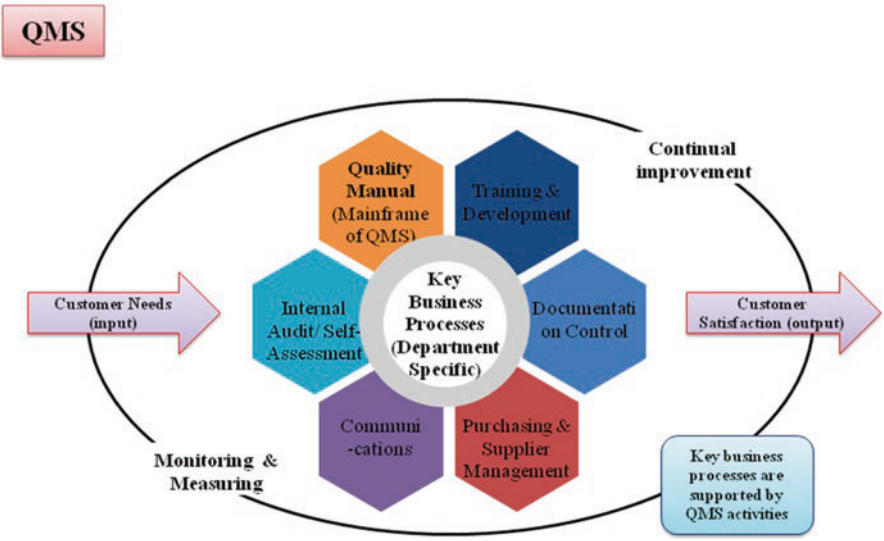


Fig. 2 Quality management system cycle

5. **Responsibility of Management**

5.1. ***Commitment of Management***

- Ensure quality policy and quality objectives and conduct management review.

5.2. ***Customer Focus***

- To make sure customer and regulatory requirements are met

5.3. ***Quality Policy***

- To make sure commitment to comply with requirements, quality objectives should be reviewed periodically to ensure appropriateness.

5.4. ***Planning***

- Objectives of quality are measurable with quality policy and QMS plan.

5.5. ***Responsibility, Authority, and Communication***

- Define responsibilities and authorities; identify management responsibility; establish appropriate communication processes.

5.6. ***Management Review (Changes in Input and Outputs)***

- Document procedures for management review; list inputs for review; record output review.

6. **Management Resource**

6.1. ***Resource Provisions***

- To determine and give resources to maintain QMS and to meet up applicable regulatory and customer requirements

6.2. ***Human Resources (Changes in Skills and Training)***

- Identify skills, provide training, evaluate effectiveness, and ensure awareness of personnel.

6.3. ***Infrastructure (Changes in Requirements)***

- Ensure infrastructure prevents product mix and orderly handling of product.
- Infrastructure includes building, workspace, process equipment, and supporting service (transport, communication, or information services).

6.4. ***Work Environment and Contamination Control***

6.4.1. ***Work Environment***

- To document requirements for work environment to maintain health, cleanliness, and clothing.

6.4.2. ***Contamination Control (New Subclause)***

- The sterile medical device requirements to control contamination with microorganisms or particulate matter

7. **Product Realization**

7.1. ***Product Realization Planning (Added to List)***

- Document process for risk management.
- Ensure quality objectives and requirements for product.
- Provide resources, infrastructure, and work environment.
- Determine verification, validation, monitoring, measurement, inspection, test, handling, storage, distribution, and traceability activities related to the product.
- Maintain records.

7.2. ***Processes Related to Customer***

7.2.1. ***Determination of Product-Related Requirements***

- Requirement defined by customer including delivery and post-delivery activities
- Regulatory requirement, user training, any other additional requirements

7.2.2. ***Review of Product Requirements***

- Ensure capability to meet the defined requirement.

7.2.3. ***Communication***

- Plan and document communication with customer on product info, enquiries, contracts, handling orders, feedbacks, and advisory notices.

7.3. ***Design and Development (Fig. 3)***

7.3.1. ***Design and Development Transfer (New Subclause)***

- Transfer documented procedures of design and development outputs to manufacturing.

7.3.2. ***Design Control and Development Changes***

- To identify changes and to maintain records, to review, to verify, to validate, and to approve before implementing

7.3.3. ***Design and Development of Files (New Subclause)***

- Maintain design and development files for every medical device type or medical device family.

7.4. ***Purchasing***

7.4.1. ***Process of Purchasing (New Added)***

- Evaluation criteria and selection of suppliers
- Monitoring and re-evaluation of suppliers

7.4.2. ***Purchasing Information (New Added)***

- Information on product specifications, product acceptance, qualification of supplier personnel
- Notification changes to purchased products

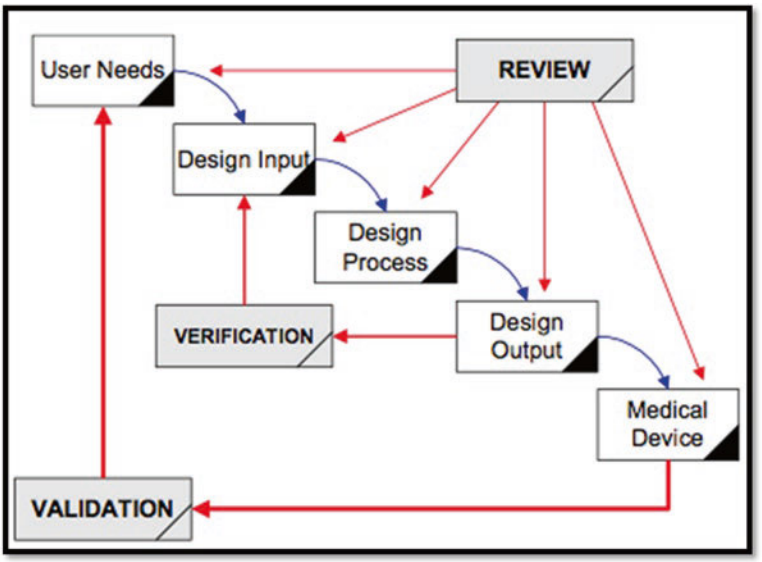


Fig. 3 Design and development process of medical device

7.4.3. ***Purchased Product Verification (New Added)***

- Inspection process and actions to be taken on changes to the purchased product

7.5. ***Production and Provision for Service***

7.5.1. ***Production Control and Service Provision (New Added)***

- Monitoring and measuring process parameters, availability of equipment, implementation of operations such as labeling and packaging

7.5.2. ***Product Cleanliness (New Added)***

- Clean prior to sterilization, supplied non-sterile and cleaning at customer end.

7.5.3. ***Installation Activities***

- Req's on installation of product

7.5.4. ***Servicing Activities (New Req's Added)***

- Servicing procedures analyze records.

7.5.5. ***Requirements Particular for Sterile Medical Devices***

- Sterilization process parameters

7.5.6. ***Processes for Production Validation and Provision for Service (New Added)***

- Special processes

7.5.7. ***Particular Requirements for Process Validation for Sterilization and for Sterile Barrier Systems (New Added)***

- Document procedures for the validation of processes.

7.5.8. ***Identification (New Req's Added)***

- Unique device identification (UDI)

7.5.9. ***Traceability***

- Through records of components, materials, and conditions for the work environment used

7.5.10. ***Customer Property***

- To identify, verify, protect, and safeguard customer property

7.5.11. ***Preservation of Product (New Added)***

- Preserve during processing, storage, handling, and distribution.
- Protect from alteration, contamination, or damage.

7.6. ***Monitoring Control and Measuring Equipment***

- Calibration of monitoring and measurement equipment
- Protected from damage

- Records maintenance
- Procedure for validation of computer software application used for monitoring and measurements of requirements

8. **Measurement, Analysis, and Improvement**

8.1. ***General***

- Conformity to product and QMS

8.2. ***Monitoring and Measurement***

8.2.1. ***Feedback***

- To monitor the quality, feedback document procedures serves as a main input.

8.2.2. ***Complaint Handling (New Subclause)***

- Receive, record, analyze, investigate, and initiate corrective and prevention action (CAPA).

8.2.3. ***Reporting to Regulatory Authorities (New Subclause)***

- Report adverse events.

8.2.4. ***Internal Audit***

- Ensure Quality management system (QMS) is effectively maintained, planned intervals.

8.2.5. ***Monitoring and Measurement of Processes***

- Methods for QMS process monitoring

8.2.6. ***Monitoring and Measurement of Product***

- To verify product requirements met evidence of conformity to acceptance criteria

8.3. ***Nonconforming Product Control (New Added)***

8.3.1. ***General***

- Identification and control of nonconforming product

8.3.2. ***Actions Response to Nonconforming Product Detected Before Delivery***

- Eliminate detected nonconformity.

8.3.3. ***Actions Response to Nonconforming Product Detected After Delivery***

- Take actions; issue advisory notices.

8.3.4. ***Rework***

- Undergo same review and approval.

8.4. ***Analysis of Data (New Req's Added)***

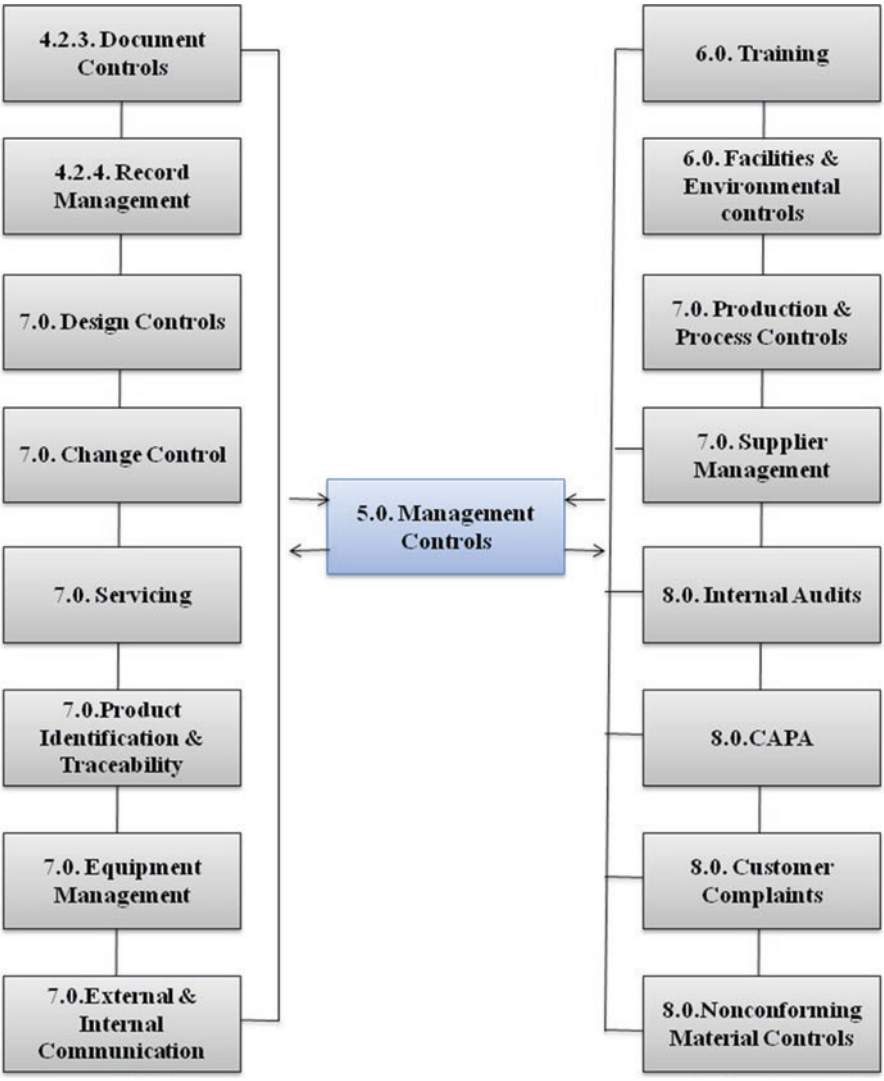


Fig. 4 QMS layout process. (Courtesy: David N. Muchemu. Designing a world-class quality management system for FDA regulated industries: Quality system requirements (QSR) for cGMP. Author House Publisher, Bloomington, Indiana; 2008: Page: 14)

- Statistical techniques to analyze data

8.5. ***Improvement: Corrective Action and Preventive Action (New Req's Added)***

- Eliminate causes of potential nonconformities (Fig. 4).

Effective on 1 March 2018, ISO 13485:2003 certificates published as an ISO standard on 1 March 2016 will no longer be issued, modified, or revised. Once ISO 13485:2016 published reviewed accepted and voted for Harmonization in Europe.

EU harmonized standards are recognized for "presumed compliance" with EU medical directive requirements (e.g., EN ISO 13485:2016 for CE marketing).

Medical Device Regulation

There are more detailed requirements on everything: previous MD Directive 60+ pages versus new regulation of 566 pages. It will greatly change how approval for products is sought and maintained. Software in a medical device helps in assuring medical device regulation. Established product must comply with this, so standards were used in product development and clinical trial carried out and to rule out market supply issues. This is equivalence level to predicate and contract in place, disproportionately affect start-ups/smaller companies, reduce the number of new products. Some devices will be up classified.

Medical device regulations also deals with clinical data requirements, common specifications, unique device identification system, person responsible, revised economic operator roles, general safety and performance requirements, cosmetic devices/devices without an indented medical purpose, and unannounced audits: MDR states at least once every 5 years. In Europe, additional medical device Periodic Safety Update Reports (PSUR) and Post-Market Surveillance Reports (PMSR) are required.

References

1. David N. Muchemu. Designing a world-class quality management system for FDA regulated industries: Quality system requirements (QSR) for cGMP. Author House Publisher, Bloomington, Indiana; 2008: Pages: 14–43. (ISBN-978-1-4343-4871-5 (sc); ISBN-13:978-1-4343-4872-2(hc))
2. Medical devices—Quality management systems—Requirements for regulatory purposes. Third edition. ISO 13485:2016(E)-03-01
3. Case Study: Clearing the Path to EU MDR Compliance.

ISO 14971 and ISO 24971: Medical Device Risk Management

Thamizharasan Sampath, Sandhiya Thamizharasan, K. Vijay Kumar Shetty, and Prakash Srinivasan Timiri Shanmugam

Abbreviations

CMR	Carcinogenic, mutagenic and toxic for reproduction
EDs	Endocrine disruptors
ISO	International Organization for Standardization
PBT	Persistent bioaccumulative toxic
vPvB	Very persistent and very bioaccumulative

Highlights

- This chapter covers the importance and applications of risk analysis and risk management process of medical devices.
- It also elucidates ISO regulations to minimize use-related hazards and assure that intended users are able to use medical devices safely and effectively.

1 Introduction

Medical devices developed for human application are used for diagnostic or treatment purposes. They may either be an instrument, an apparatus or a material. Moreover, these devices can be used for daily patient care as well as for medical scientific purposes. Researchers in charge to develop new medical devices are faced

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

K. Vijay Kumar Shetty
Department of Pharmacology, Zydus Medical College and Hospital, Dahod, Gujarat, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_3

with the complex task of making a medical device safe for human use. This implies that the device should be safe and effective. Risk management involves the identification, understanding, control and prevention of failures that can result in hazards when people use medical devices. Risk analysis plays a key role in the development of medical devices design. Risk analysis, or hazard analysis, is a structured tool for the evaluation of potential problems which could be encountered in connection with the use of taking a drug, or using a medical device. Manufacturers are expected to identify possible hazards associated with the design in both normal and fault conditions. If any risk is judged unacceptable, it should be reduced to acceptable levels by appropriate means. The latest version of ISO 14971:2019 ("Medical devices – Application of risk management to medical devices") was approved on 2 May 2019 by the Association for the Advancement of Medical Instrumentation (AAMI) and on 10 May 2019 by the American National Standards Institute (ANSI).

ISO 14971:2019

2 Scope

It is the specified standard for risk management used to demonstrate compliance with the risk management requirements of the medical devices. This international standard specifies a process for a manufacturer to identify the hazards associated with medical devices, including in vitro diagnostic (IVD) medical devices, to estimate and evaluate the associated risks, to control these risks and to monitor the effectiveness of the controls. The standard addresses risk management to patient, operator, other parties, external equipment and/or the environment. Risk Management Process ISO 14971 requires the manufacturer to establish, document and maintain a risk management process for:

- Reviewing the intended use (intended purpose) of the medical device
- Identification of hazards (known and foreseeable)
- Estimation of the probability of occurrence of harm
- Estimation of the severity of each hazard and its harm
- Evaluation of associated risks (decision-making)
- Control of these risks
- Monitoring of the effectiveness of these controls throughout the whole life cycle of a medical device
- This international standard does not apply to decisions on the use of a medical device in the context of any particular clinical procedure or business risk management.
- This international standard does not specify acceptable risk levels.

The risk management process does not end with the design and manufacturing process but also includes applicable sterilization, packaging, labelling, storage, handling/transport, distribution and market surveillance. The manufacturer shall apply

risk management from the initial conception until the ultimate decommissioning and disposal of the product. Therefore, the gathering of post-production information is a required part of the process.

3 Terms and Definitions

Accompanying documentation: materials accompanying a medical device and containing information for the user or those accountable for the installation, use, maintenance, decommissioning and disposal of the medical device particularly regarding safe use

Benefit: positive impact or desirable outcome of the use of a medical device on the health of an individual, or a positive impact on patient management or public health

Harm: injury or damage to the health of people, or damage to property or the environment

Hazard: potential source of harm

Hazardous situation: circumstance in which people, property or the environment is exposed to one or more hazards

Intended use: use for which a product, process or service is intended according to the specifications, instructions and information provided by the manufacturer

In vitro diagnostic medical device: whether used alone or in combination, intended by the manufacturer for the in vitro examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes and including reagents, calibrators, control materials, specimen receptacles, software and related instruments or apparatus or other articles

Life cycle: series of all phases in the life of a medical device from the initial conception to final decommissioning and disposal

Manufacturer: natural or legal person with responsibility for the design and/or manufacture of a medical device with the intention of making the medical device available for use, under his name, whether or not such a medical device is designed and/or manufactured by that person himself or on his behalf by another person(s)

Medical device: instrument, apparatus, implement, machine, appliance, implant, reagent for in vitro use, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings, for one or more of the specific medical purposes of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury
- Investigation, replacement, modification or support of the anatomy or of a physiological process
- Supporting or sustaining life

- Control of conception
- Disinfection of medical devices
- Providing information by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means

Objective evidence: data supporting the existence or verity of something

Post-production: part of the life cycle of the medical device after the design has been completed and the medical device has been manufactured, for example, transportation, storage, installation, product use, maintenance, repair, product changes, decommissioning and disposal

Procedure: specified way to carry out an activity or a process

Process: set of interrelated or interacting activities that use inputs to deliver an intended result

Reasonably foreseeable misuse: use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behaviour

Record: document stating results achieved or providing evidence of activities performed

Residual risk: risk remaining after risk control measures have been implemented

Risk: combination of the probability of occurrence of harm and the severity of that harm

Risk analysis: systematic use of available information to identify hazards and to estimate the risk

Risk assessment: overall process comprising a risk analysis and a risk evaluation

Risk control: process in which decisions are made and measures implemented by which risks are reduced to, or maintained within, specified levels

Risk estimation: process used to assign values to the probability of occurrence of harm and the severity of that harm

Risk evaluation: process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

Risk management: systematic application of management policies, procedures and practices to the tasks of analysing, evaluating, controlling and monitoring risk

Risk management file: set of records and other documents that are produced by risk management

Safety: freedom from unacceptable risk

Severity: measure of the possible consequences of a hazard

State of the art: developed stage of technical capability at a given time as regards products, processes and services, based on the relevant consolidated findings of science, technology and experience

Top management: person or group of people who directs and controls a manufacturer at the highest level

Use error: user action or lack of user action while using the medical device that leads to a different result than that intended by the manufacturer or expected by the user

Verification: confirmation, through the provision of objective evidence that specified requirements have been fulfilled

4 General Requirements for Risk Management

Risk management involves the identification, understanding, control and prevention of failures that can result in hazards when people use medical devices. Manufacturers are expected to identify possible hazards associated with the design in both normal and fault conditions. The risks associated with the hazards, including those resulting from user error, should be calculated in both normal and fault conditions. If any risk is judged unacceptable, it should be reduced to acceptable levels by appropriate means.

Risk Management Process
The manufacturer shall establish, implement, document and maintain an ongoing process for:

(a) Identifying hazards and hazardous situations associated with a medical device
(b) Estimating and evaluating the associated risks
(c) Controlling these risks
(d) Monitoring the effectiveness of the risk control measures

This process shall apply throughout the life cycle of the medical device. This process shall include the following elements:

– Risk analysis
– Risk evaluation
– Risk control
– Production and post-production activities

4.1 Competence of Personnel

Persons performing risk management tasks shall be competent on the basis of education, training, skills and experience appropriate to the tasks assigned to them. Where appropriate, these persons shall have knowledge of and experience with the particular medical device (or similar medical devices) and its use, the technologies involved or the risk management techniques employed. Appropriate records shall be maintained. Compliance is checked by inspection of the appropriate records (Fig. 1).

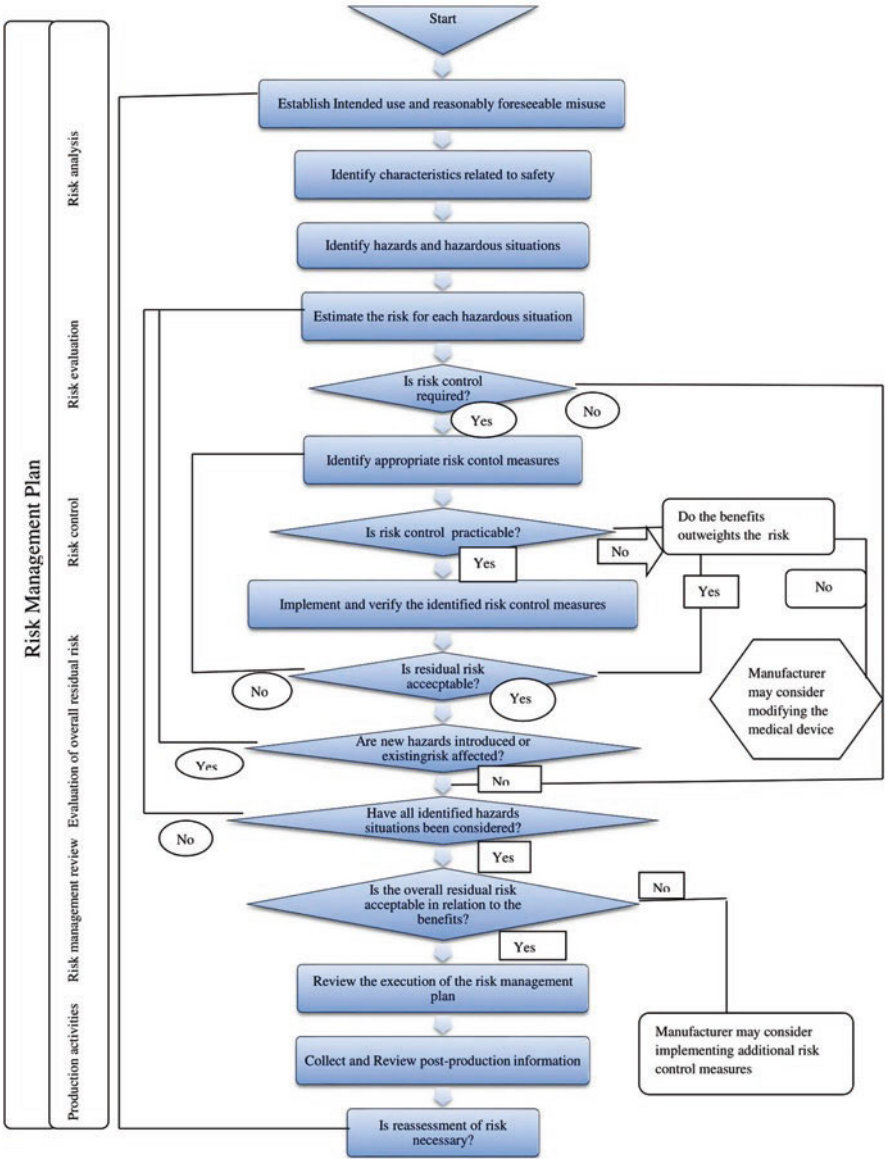


Fig. 1 Schematic representation of risk management process

4.2 Risk Management Plan

Risk management activities shall be planned for the particular medical device being considered; the manufacturer shall establish and document a risk management plan in accordance with the risk management process. The risk management plan shall be part of the risk management file. This plan shall include the following:

(a) The scope of the planned risk management activities, identifying and describing the medical device and the life cycle phases for which each element of the plan is applicable.
(b) Assignment of responsibilities and authorities.
(c) Requirements for review of risk management activities.
(d) Criteria for risk acceptability, based on the manufacturer's policy for determining acceptable risk, including criteria for accepting risks when the probability of occurrence of harm cannot be estimated. The criteria for risk acceptability are essential for the ultimate effectiveness of the risk management process. For each risk management plan, the manufacturer needs to establish risk acceptability criteria that are appropriate for the particular medical device.
(e) A method to evaluate the overall residual risk and criteria for acceptability of the overall residual risk based on the manufacturer's policy for determining acceptable risk. It includes gathering and reviewing data and literature for the medical device being considered and similar medical devices on the market and can involve judgment by a cross-functional team of experts with application knowledge and clinical expertise.
(f) Activities for verification of the implementation and effectiveness of risk control measures.
(g) Activities related to collection and review of relevant production and post-production information.

If the plan changes during the life cycle of the medical device, a record of the changes shall be maintained in the risk management file. Compliance is checked by inspection of the risk management file.

4.3 Risk Management File

For the particular medical device being considered, the manufacturer shall establish and maintain a risk management file. In addition to the requirements of other clauses of this document, the risk management file shall provide traceability for each identified hazard to:

– The risk analysis
– The risk evaluation
– The implementation and verification of the risk control measures
– The results of the evaluation of the residual risks

The records and other documents that make up the risk management file can form part of other documents and files required, for example, by a manufacturer's quality management system. The risk management file need not physically contain all the records and other documents. However, it needs to contain at least references or pointers to all required documentation, so that the manufacturer can assemble the information referenced in the risk management file in a timely manner.

5 Risk Analysis

The manufacturer shall perform risk analysis for the particular medical device. The implementation of the planned risk analysis activities and the results of the risk analysis shall be recorded in the risk management file. If a risk analysis or other relevant information is available for a similar medical device, that analysis or information can be used as a starting point for the new risk analysis. The degree of relevance depends on the differences between the medical devices and whether these introduce new hazards or significant differences in outputs, characteristics, performance or results. The extent of use of an existing risk analysis is based on a systematic evaluation of the effects that the differences can have on the occurrence of hazardous situations. In addition, the documentation of the conduct and results of the risk analysis shall include at least the following:

(a) Identification and description of the medical device that was analysed
(b) Identification of the person(s) and organization who carried out the risk analysis
(c) Scope and date of the risk analysis

5.1 Intended Use and Reasonably Foreseeable Misuse

The manufacturer shall document the intended use of the particular medical device being considered. The intended use should take into account information such as the intended medical indication, patient population, part of the body or type of tissue interacted with, user profile, use environment and operating principle. The manufacturer shall also document reasonably foreseeable misuse.

5.2 Identification of Characteristics Related to Safety

For the particular medical device being considered, the manufacturer shall identify and document those qualitative and quantitative characteristics that could affect the safety of the medical device. Where appropriate, the manufacturer shall define limits of those characteristics. This documentation shall be maintained in the risk management file. Characteristics related to loss or degradation of the clinical performance of a medical device that can result in unacceptable risk are sometimes referred to as essential performance.

5.3 Identification of Hazards and Hazardous Situations

The manufacturer shall identify and document known and foreseeable hazards associated with the medical device based on the intended use, reasonably foreseeable misuse and the characteristics related to safety in both normal and fault conditions. For each identified hazard, the manufacturer shall consider the reasonably foreseeable sequences or combinations of events that can result in a hazardous situation and shall identify and document the resulting hazardous situations (Fig. 2 and Tables 1, 2 and 3).

5.4 Risk Estimation

For each identified hazardous situation, the manufacturer shall estimate the associated risk(s) using available information or data. For hazardous situations for which the probability of the occurrence of harm cannot be estimated, the possible consequences shall be listed for use in risk evaluation and risk control. The results of these activities shall be recorded in the risk management file. The system used for qualitative or quantitative categorization of probability of occurrence of harm and severity of harm shall be recorded in the risk management file. Risk estimation incorporates an analysis of the probability of occurrence of harm and the severity of the harm. Depending on the area of application, only certain elements of the risk estimation process might need to be considered in detail. For example, when the harm is minimal, an initial hazard and consequence analysis could be sufficient, or when insufficient information or data are available, a conservative estimate of the

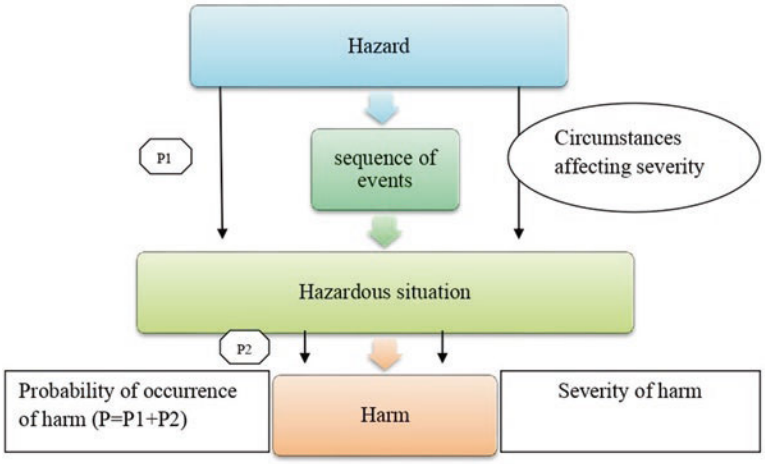


Fig. 2 Hazard and sequence of events

Table 1 Examples of hazards

Energy hazards	Biological & Chemical hazards	Performance related hazards
Acoustic energy	*Biological agents*	*Data*
Infrasound	Bacteria	Access
Sound pressure	Fungi	Availability
Ultrasonic	Parasites	Confidentiality
Electric energy	Prions	Transfer
Electric fields	Toxins	Integrity
Leakage current	Viruses	*Delivery*
Earth leakage	*Chemical agents*	Quantity
Enclosure leakage	Carcinogenic, mutagenic, reproductive causative, corrosive	Rate
Magnetic fields		*Diagnostic information*
Static discharge	Acidic	Examination result
Voltage	Alkaline	Image artefacts
Mechanical energy	Oxidants	Stock orientation
Kinetic energy	Flammable, combustible, explosive	Image resolution
Falling objects	fumes and vapors	Patient identity
High pressure fluid injection	Particles(including micro and nano particles)	Patient identity/ information
		Functionality
Moving parts	Pyrogenic	Alarm
Vibrating parts	Solvents	Critical performance
Potential energy	Toxic	Measurement
Bending	Asbestos	
Compression	Heavy metals	
Cutting, shearing	Inorganic toxicants	
Gravitational pull	Silica	
Suspended mass	*Immunological agents*	
Tension	Allergenic	
Torsion	Antiseptic substances	
Radiation energy	Latex	
Ionizing radiation	Immunosuppressive irritants	
Accelerated particles(alpha particles, electrons,protons,neutrons)	Cleaning residue sensitizing	
Gamma		
x-ray		
Non-ionizing radiation		
Infrared		
Laser		
Microwave		

(continued)

Table 1 (continued)

Energy hazards	Biological & Chemical hazards	Performance related hazards
Ultraviolet		
Thermal energy		
Cryogenic effects		
Hyperthermic effects		

Table 2 Examples of events and circumstances

General category	Events and circumstances
Requirements	Inadequate specification of
	Design parameters
	Operating parameters
	Performance requirements
	In service requirements (e.g. maintenance, reprocessing)
Manufacturing process	Insufficient control of
	Manufacturing process
	Changes to manufacturing process
	Materials
	Materials compatibility information
	Subcontractors
Transport and storage	Inadequate packaging
	Contamination or deterioration
	Inappropriate environment conditions
Environmental factors	Physical factors (e.g. heat, pressure, time)
	Chemical factors (e.g. corrosion, degradation, contamination)
	Electromagnetic fields (e.g. susceptibility to electromagnetic disturbance)
	Inadequate supply of power
	Inadequate supply of coolant
Cleaning disinfection and sterilization	Lack of validated procedures
	Inadequate specification of requirements
	Inadequate performance of cleaning, disinfection or sterilization
Disposal and scrapping	No or inadequate information provided
	Use error
Formulation	Biodegradation
	Biocompatibility
	No information or inadequate specification provided
	Incorrect formulations
	Use error
Usability	Confusing or missing instructions for use
	Complex or confusing control system
	Ambiguous or unclear presentation of setting measurements or other information

(continued)

Table 2 (continued)

General category	Events and circumstances
	Misrepresentation of results
	Insufficient visibility, audibility or tactility
	Poor mapping of controls to actions or displayed information to actual state
	Controversial modes or mapping as compared to existing equipment
	Use by unskilled or untrained personnel
	Insufficient warming of side effects
	Inadequate warming of hazards associated with re use of single use medical devices
	Incorrect measurement and other meteorological aspects
	Incompatibility with consumables, accessories other medical devices
	Incorrect patient identification
	Slips, lapses and mistakes
Functionality	Loss of electrical or mechanical integrity
	Deterioration in performance (e.g. gradual occlusion of fluid change in resistance to flow electrical conduction) as a result of ageing wear and repeated use.
Security	Unsecured data ports that are externally accessible (e.g. network, serial or USB ports) Data without encryption
	Software vulnerabilities that can be exploited

Table 3 Relationship between hazards, foreseeable sequences of events, hazardous situation and harm

Hazard	Foreseeable sequences of events	Hazardous situations	Harm
Electromagnetic energy (high voltage)	(1) Electrode cable unintentionally plugged into power line receptacle	Line voltage appears on electrodes	Serious burns Heart fibrillation
Chemical (voltatile solvent, embolus)	(1) Incomplete removal of volatile solvent used in manufacuring	Development of gas embolism (bubbles in the blood stream) during dialysis	Infarct Brain damage
	(2) Solvent residue converts to gas at body temperature		
Biological (microbial contamination)	(1) Inadequate instructions provided for decontaminating re-used anaesthesia tubing	Bacteria released into airway of patient during anaesthesia	Bacterial infection
	(2) Contaminated tubing used during anaesthesia		

(continued)

Table 3 (continued)

Hazard	Foreseeable sequences of events	Hazardous situations	Harm
Functionality (no delivery)	(1) Electrostatically charged patient touches infusion pump	Failure to deliver insulin to patient with elevated blood glucose level, no warning given	Minor organ damage
			Decreased
	(2) Electrostatically discharged (ESD) causes pump and pump alarms to fail		Consciousness
Functionally (no output)	(1) Implantable defibrillator battery reaches the end of its useful life	Defibrillator cannot deliver shock when an arrhythmia occurs	Death
	(2)Inappropriately long interval between clinical follow up visits		
Measurement (Incorrect information)	(1) Measurement error	Incorrect information Reported to clinician, leading to misdiagnosis and /or lack of proper therapy	Progression of disease
	(2) No detection by user		Serious injury

probability of occurrence can give some indication of the risk. Information or data for estimating risks can be obtained from:

- Published standards
- Scientific or technical investigations
- Field data from similar medical devices already in use
- Usability tests employing typical users
- Clinical evidence
- Results of relevant investigations or simulations
- Expert opinion
- External quality assessment schemes for in vitro diagnostic medical devices

6 Risk Evaluation

For each identified hazardous situation, the manufacturer shall evaluate the estimated risks and determine if the risk is acceptable or not, using the criteria for risk acceptability defined in the risk management plan. If the risk is acceptable, it is not required to apply the requirements given in the risk control process to this hazardous situation, and the estimated risk shall be treated as residual risk. If the risk is not acceptable, then the manufacturer shall perform risk control activities. The results of this risk evaluation shall be recorded in the risk management file.

7 Risk Control

7.1 Risk Control Option Analysis

The manufacturer shall determine risk control measures that are appropriate for reducing the risks to an acceptable level. The manufacturer shall use one or more of the following risk control options in the priority order listed:

(a) Inherently safe design and manufacture
(b) Protective measures in the medical device itself or in the manufacturing process
(c) Information for safety and, where appropriate, training to users

The risk control measures selected shall be recorded in the risk management file. During risk control analysis, the manufacturer determines that risk reduction is not practicable; the manufacturer shall conduct a benefit-risk analysis of the residual risk.

7.2 Implementation of Risk Control Measures

The manufacturer shall implement the risk control measures selected in the risk control option. Implementation of each risk control measure shall be verified.

Verification of effectiveness can also be performed as part of design and development verification or process qualification, if the relationship between the effectiveness in risk reduction and the result of design and development verification or process qualification is known.

– Design verification of a certain performance characteristic, such as dose accuracy of a drug injector, can serve as verification of effectiveness of risk control measures ensuring safe drug dosing.
– Process qualification can serve as verification of effectiveness of risk control measures related to risk caused by variations in production output.

7.3 Residual Risk Evaluation

After the risk control measures are implemented, the manufacturer shall evaluate the residual risk using the criteria for risk acceptability defined in the risk management plan. The results of this evaluation shall be recorded in the risk management file. If a residual risk is not judged acceptable using these criteria, further risk control measures shall be considered.

7.4 Benefit-Risk Analysis

If a residual risk is not judged acceptable using the criteria established in the risk management plan and further risk control is not practicable, the manufacturer may gather and review data and literature to determine if the benefits of the intended use outweigh this residual risk. If this evidence does not support the conclusion that the benefits outweigh this residual risk, then the manufacturer may consider modifying the medical device or its intended use. Otherwise, this risk remains unacceptable. If the benefits outweigh the residual risk, then proceed to risk control measures.

7.5 Risks Arising from Risk Control Measures

The manufacturer shall review the effects of the risk control measures with regard to whether new hazards or hazardous situations are introduced or the estimated risks for previously identified hazardous situations are affected by the introduction of the risk control measures. Any new or increased risks shall be managed in accordance with risk management protocol. The manufacturer shall also review the risk control activities to ensure that the risks from all identified hazardous situations have been considered and all risk control activities are completed.

7.6 Evaluation of Overall Residual Risk

After all risk control measures have been implemented and verified, the manufacturer shall evaluate the overall residual risk posed by the medical device, taking into account the contributions of all residual risks, in relation to the benefits of the intended use, using the method and the criteria for acceptability of the overall residual risk defined in the risk management plan. If the overall residual risk is judged acceptable, the manufacturer shall inform users of significant residual risks and shall include the necessary information in the accompanying documentation in order to disclose those residual risks. If the overall residual risk is not judged acceptable in relation to the benefits of the intended use, the manufacturer may consider implementing additional risk control measures or modifying the medical device or its intended use. Otherwise, the overall residual risk remains unacceptable.

8 Risk Management Review

Prior to release for commercial distribution of the medical device, the manufacturer shall review the execution of the risk management plan. This review shall at least ensure that:

– The risk management plan has been appropriately implemented
– The overall residual risk is acceptable
– Appropriate methods are in place to collect and review information in the production and post-production phases

The manufacturer shall establish, document and maintain a system to actively collect and review information relevant to the medical device in the production and post-production phases. When establishing this system, the manufacturer shall consider following methods for the collection and processing of information.

– Information generated during production and monitoring of the production process
– Information generated by the user
– Information generated by those accountable for the installation, use and maintenance of the medical device
– Information generated by the supply chain
– Publicly available information
– Information related to the generally acknowledged state of the art

The manufacturer shall review the information collected for possible relevance to safety, especially whether:

– Previously unrecognized hazards or hazardous situations are present
– An estimated risk arising from a hazardous situation is no longer acceptable
– The overall residual risk is no longer acceptable in relation to the benefits of the intended use
– The generally acknowledged state of the art has changed

The collected information is determined to be relevant to safety; the following actions apply:

Concerning the particular medical device, the manufacturer shall review the risk management file and determine if reassessment of risks and/or assessment of new risk is necessary. If a residual risk is no longer acceptable, the impact on previously implemented risk control measures shall be evaluated and should be considered as an input for modification of the medical device and shall evaluate the impact on previously implemented risk management activities, and the results of this evaluation shall be considered as an input for the review of the suitability of the risk management process by top management.

9 ISO/TR 24971:2013: Guidance on Application of ISO 14971

Aim and Scope

ISO/TR 24971 has the same structure and numbering of clauses as the revision of ISO 14971. Guidance is provided to help understand and implement each

requirement in ISO 14971. This new structure should make the guidance more relevant and easier to navigate. Annexes to the guidance in ISO/TR 24971 have been prepared to provide more detailed approaches to specific aspects of risk management. The annexes include the following:

- Identification of hazards and characteristics of safety provides questions that can aid in identifying the characteristics of the medical device that could affect safety.
- Risk analysis techniques provide guidance on some available tools that support the performance of a risk analysis but emphasize that these techniques do not include all steps of the risk management process.
- Risk acceptability considerations describe aspects that can be used as part of risk control options analysis and be applied to risks for which the probability cannot be estimated.
- Information for safety and information on residual risk seek to clarify the differences between "information for safety" and "disclosure of residual risk". It also provides guidance on information for safety as a risk control measure and how residual risks can be disclosed to promote risk awareness.
- Guidance on risks related to (cyber)security outlines terminology used in security risk management and the relationship between ISO 14971 and (cyber)security risks.
- Components and devices designed not using ISO 14971 aim to address preparing a risk management file retrospectively. It addresses how to build an initial risk management file when all the processes and requirements described in ISO 14971 were not followed at the time when the device was initially designed. This could be applicable for medical devices already available on the market or for constituent components of a medical device, such as subsystems of non-medical origin.
- Guidance for in vitro diagnostic medical devices is focused on the indirect risks to patients from incorrect or delayed in vitro diagnostic results.

9.1 International Product Safety Standards in Risk Management

International product safety and process standards play a significant role in risk management as described by ISO 14971. In principle, these standards are developed using a type of risk management that can include identifying hazards and hazardous situations, estimating risks, evaluating risks and specifying risk control measures. When performing risk management activities, manufacturers can take advantage of the work of the standards writers and need not repeat the analyses leading to the requirements of the standard. International standards, therefore, provide valuable information on risk acceptability that has been validated during a worldwide evaluation process, including multiple rounds of review, comment and voting.

An international product safety standard can establish requirements that, when implemented, result in acceptable risk for specific hazardous situations (e.g. safety limits). The manufacturer can apply these requirements in the following way when managing risk:

(a) Where an international product safety standard specifies technical requirements addressing particular hazards or hazardous situations, together with specific acceptance criteria, compliance with those requirements is presumed to establish that the residual risks have been reduced to acceptable levels unless there is objective evidence to the contrary. For example, in IEC 60601-1, Medical electrical equipment – Part 1: General requirements for basic safety and essential performance, leakage current must be controlled to achieve an acceptable level of risk. IEC 60601-1 provides leakage current limits that are considered to result in an acceptable level of risk when measured under the conditions stated in 8.7 of IEC 60601-1:2005. For this example, further risk management would not be necessary. The following steps need to be taken in this case:

   (i) Identify characteristics related to safety and identify hazards and hazardous situations associated with the device as completely as possible.
   (ii) Identify those hazards and hazardous situations relevant to the particular medical device that are exactly covered by the international product safety standard.
   (iii) For those identified hazards and hazardous situations exactly covered by the international product safety standard, the manufacturer may choose not to estimate or evaluate the risks so identified but rather rely on the requirements contained in the international standard to demonstrate the completion of risk estimation and risk evaluation.
   (iv) To the extent possible, the manufacturer should identify the design specifications that satisfy the requirements in the standard and serve as risk control measures.
   (v) Verification of the implementation of the risk control measures for these hazardous situations is obtained from the design documents. Verification of the effectiveness of the risk control measures is obtained from the tests and test results demonstrating that the device meets the relevant requirements of the international product safety standard.
   (vi) If the relevant requirements are met, the associated residual risk is considered acceptable.

(b) Where an international product safety standard does not completely specify technical requirements and associated tests and test acceptance criteria, the situation is more complex. In some cases, the standard directs the manufacturer to perform specific tests related to known hazards or hazardous situations but does not provide specific test acceptance criteria (e.g. IEC 60601-2-16, Medical electrical equipment: Particular requirements for basic safety and essential per-

formance of haemodialysis, haemodiafiltration and haemofiltration equipment). In some other cases, the standard can simply direct the manufacturer to investigate specific hazards or hazardous situations in their risk analysis (IEC 60601-1:2005). The range of alternatives is too large to provide specific guidance on how to use such standards in the risk management process. Manufacturers are encouraged, however, to use the content of such standards in their risk management of the particular medical device.

(c) For hazards or hazardous situations that are identified for the particular medical device but are not specifically addressed in any standard, the manufacturer needs to address those hazards or hazardous situations in the risk management process.

International Process Standards and ISO 14971

International process standards, as shown in the examples below, can often be used in conjunction with ISO 14971. This is performed in one of two ways: The international process standard requires application of ISO 14971 as part of the implementation of the international process standard, e.g. IEC 62304 on software life cycle processes; or the international process standard is intended to be used in risk management, e.g. IEC 62366 on usability engineering and the ISO 10993 series on biological evaluation. In either case, proper use of the international process standard requires attention to the interfaces between that standard and ISO 14971 in order to achieve acceptable levels of risk for the medical device. The two standards should work together such that inputs, outputs and their timing are optimized. Three examples are given below to demonstrate this ideal situation.

9.2 IEC 62304: Medical Devices Software Life Cycle Processes

The risk management process is already very well addressed by the international standard ISO 14971. Therefore IEC 62304 makes use of this advantage simply by a normative reference to ISO 14971. Some minor additional risk management requirements are needed for software, especially in the area of identification of contributing software factors related to hazards. Whether software is a contributing factor to a hazard is determined during the hazard identification activity of the risk management process. Hazards that could be indirectly caused by software (e.g. by providing misleading information that could cause inappropriate treatment to be administered) need to be considered when determining whether software is a contributing factor. The decision to use software to control risk is made during the risk control activity of the risk management process. The software risk management process required in this standard has to be embedded in the device risk management process according to ISO 14971.

9.3 IEC 62366: Application of Usability Engineering to Medical Devices

IEC 62366:2007 identifies specific clauses where the usability engineering process can supplement and interact with risk management as described in ISO 14971. It requires the following: “An identification of characteristics related to safety (part of a risk analysis) that focuses on usability shall be performed and “The manufacturer shall identify known or foreseeable hazards (part of a risk analysis) related to usability”. It makes several references to activities that would be undertaken as part of risk management.

9.4 ISO 10993: Biological Evaluation of Medical Devices

Biological safety evaluation and hazard testing of medical devices shall be performed in compliance with the ISO 10993 “Biological Evaluation of Medical Devices” series as international standards. Based on the framework and principles of ISO 10993-1 “Evaluation and Testing”, the necessary evaluation items can be selected corresponding to the nature and duration of exposure of individual medical devices with the human body. The test method guidelines in the ISO 10993 series generally include lists of multiple test methods for each evaluation item. ISO 10993-3 specifies strategies for risk estimation, selection of hazard identification tests and risk management, with respect to the possibility of the following potentially irreversible biological effects arising as a result of exposure to medical devices:

- Acute toxicity
- Chronic toxicity
- Irritation (eye, skin, mucosal surfaces)
- Hypersensitivity
- Genotoxicity
- Carcinogenicity
- Reproductive and developmental toxicity

The international standards have been continuously revised according to the development of science and technology. Accordingly, an appropriate test method must be selected, considering the most current international standards at the time when testing is conducted.

EU Regulation

EU Regulation of RoHS: European Union directives have restricted the use of certain hazardous substances in medical devices and implants. Hazardous substances are categorized per EU Regulation 1272/2008 (Classification, Labelling and Packaging of substances/mixtures and substances identified in EU Regulation

1907/2006) (REACH: Registration, Evaluation, Authorisation and Restriction of Chemicals). EU 1272/2008 REACH contains all hazardous chemicals list. SVHC (substance of very high concern) contains CMR substances like N,N-Dimethylanilinium Tetrakis (pentafluoropheny) borate, dibutyltin hydrogen borate and perboric acid and restricted substances list of EDs, PBT and vPvB. Chemicals that are substances of very high concern are to be phased out and replaced with safer alternative chemicals. In addition with CMR, EDs, PBTs and vPvB, the lists extend with flammable gas, flammable aerosol, oxidizing gas, gases under pressure, flammable liquid, flammable solid, self-reactive substance or mixture and chemicals capable of causing skin corrosion, irritation, serious eye irritation, respiratory/skin sensitization, germ cell mutagenicity, specific target organ toxicity and hazard to the aquatic environment and ozone layer. RoHS specifies maximum levels by weight for the following ten restricted materials. The first six applied to the original RoHS, while the last four phthalates were added under RoHS III. The expanded list for RoHS 3 is thus as follows:

- Lead (0.1%)
- Mercury (0.1%)
- Cadmium (0.01%)
- Hexavalent chromium (0.1%)
- Polybrominated biphenyls (PBB) (0.1%)
- Polybrominated diphenyl ethers (PBDE) (0.1%)
- **Bis(2-ethylhexyl) phthalate (DEHP) (0.1%)**
- **Butyl benzyl phthalate (BBP) (0.1%)**
- **Dibutyl phthalate (DBP) (0.1%)**
- **Diisobutyl phthalate (DIBP) (0.1%)**

As per RoHS guidelines, device designers are required to replace these chemicals in their products with less hazardous alternatives. The hazardous substances present in any of the medical device or implants should be less than 0.1 W/W of the device. Acceptable justification must be given if the CMR or endocrine-disrupting substances (e.g. lead compounds, other heavy metals, phenols) are present above 0.1 per cent by weight in these device types. The restriction of DEHP, BBP, DBP and DIBP shall apply to medical devices, including in vitro medical devices, and monitoring and control instruments, including industrial monitoring and control instruments, from 22 July 2021. Medical device manufacturers are advised to thoroughly review the conformity assessment procedures applicable to their device to avoid delays in the product review and approval process. In addition to the requirements of RoHS III (EU Directive 2015/863), medical device manufactures may be subject to other EU directives and regulations addressing the use of hazardous substances and the control of electrical and electronic waste. These include EU Directive 2012/19/EC on Waste Electrical and Electronic Equipment (II), and EU regulation (1907/2006), as well as EU directives on the disposal of batteries, and on product packaging and packaging waste. According to EU Directive (2011/65/EU), medical devices have to follow the restrictions regarding the use of hazardous substances.

9.5 Developing the Policy for Determining the Criteria for Risk Acceptability

According to 3.2 of ISO 14971:2007, top management is required to define and document the policy for determining the criteria for risk acceptability. This policy is intended to ensure the following:

- Criteria are based upon applicable national or regional regulations.
- Criteria are based upon relevant international standards.
- Criteria take into account available information such as the generally accepted state of the art and known stakeholder concerns.
- The applicable regulatory requirements in the regions where the medical device is to be marketed.
- The relevant international standards for the particular medical device or an intended use of the medical device that can help identify principles for setting the criteria for risk acceptability.
- Information on the state of the art can be obtained from review of the literature and other information on similar medical devices the manufacturer has marketed, as well as those from competing companies.
- The validated and comprehensive concerns from the main stakeholders. Some potential sources of information on the patient and clinician perspective can include news media, social media, patient forums as well as input from internal departments with expert knowledge of stakeholder concerns such as the clinical department. The manufacturer should provide guidelines for developing the actual criteria for risk acceptability to be used in the risk management plan for the particular medical device being considered.

9.6 Production and Post-production Feedback Loop

The initial risk assessment is based on experience with similar medical devices or applications on the market, or on assumptions when new medical devices are released to the market. Information received after market entry is valuable for confirming or correcting assumptions and estimates (both overestimates and underestimates), or identifying omissions made during the risk analysis and risk control phases. The feedback loop is established to collect and evaluate such information for potential relevance to medical device safety. The feedback loop should consist of the following steps:

- Observation and transmission
- Assessment
- Action

Observation and Transmission

An observation provides information on, or experience with, a medical device that should be compared against the current risk management file. The observation can come from a number of different sources each of which can have a bearing on the safety of the medical device.

- Information from manufacturing or research and development (R&D) activities within or contracted by the manufacturer
- Information from installation, servicing and/or training personnel within or contracted by the manufacturer
- Information from the use/users of the medical device (e.g. customer complaints, user surveys)
- Information from experience with competitor's medical devices through incident reports (e.g. from databases provided by local regulatory agencies to collect and generate an overview of device experience)
- Clinical information (e.g. post-market clinical trials on the manufacturer's own medical devices or other published clinical literature on competitors' and similar medical devices)
- Information on new or amended standards and regulations

For information to be relevant to a manufacturer's medical device, it need not be directly related to their own or a competitor's product. Information relating to similar medical devices with similar intended use or similar principles of operation can yield useful post-market information on the relevance of the risks of the manufacturer's medical device. When designing a means of acquiring or detecting post-market information, manufacturers should be careful not to introduce bias into the process. The means of acquiring or asking for feedback should be neutral with regard to achieving negative or positive feedback. Furthermore, feedback should include events that have occurred (including corrective action) as well as events that could occur (including preventive action). For any post-market information to be useful, it has to be communicated to the persons or department within the organization that has the responsibility and authority to compare against the current risk management file and enact change where necessary.

The means of transmission of this information will depend on the source of the information. Some information will be pulled (initiated by the manufacturer), and some information will be pushed (initiated by sources like the customer, authorities or patient). In either case, the organization should ensure that efficient communication channels are planned and established to allow for timely and accurate receipt of information. The rate at which the manufacturer pulls information from the various sources (including users) depends on the maturity of the medical device, its technology and the specific market. Various departments within the manufacturer's organization can receive and handle different kinds of information, for example:

- Customer complaints or adverse event reports
- Service and installation reports
- New or revised regulations, standards or guidance

- Production non-conformance reports

It is important that all relevant information from these groups is reviewed and distributed to that part of the manufacturer's organization with the responsibility and authority for the risk assessment. Where the probability of events (e.g. component failures) is a relevant factor contributing to the evaluation of risk, statistical trending of such events should be considered.

Assessment
Any revision to the risk assessment based on new observations should be subject to the same level of control and review as the initial risk assessment. This would include any subsequent identification of risk control measures, if required. Such controls should include review and approval by individuals in the same functions or departments as those who signed off originally. Any new safety-related observations are to be assessed using the current criteria for risk acceptability. New observations related to safety should be compared with the established risk management file to test the validity of any assumptions made. Several questions are suggested below:

(a) Is the intended use still valid?
(b) Is there an increasing trend of off-label use?
(c) Are there occurrences of misuse which were not foreseen in the original risk management process?
(d) Is there evidence of new hazards or hazardous situations not originally identified in the hazard identification process?
(e) Are the severity and probability estimations for a particular risk still valid?
(f) Is there any evidence that the criteria for risk acceptability should be adjusted?
(g) Is the effectiveness of risk control measures proven adequate?
(h) Does the risk/benefit analysis accurately represent the actual market experience?

If data suggest correction or adjustment of the current risk management file, the residual risks need to be evaluated based on the new data. In addition, the overall residual risk of the device should be reviewed.

Information for Safety Information for safety is regarded as a risk control measure. It is the least preferred option after inherent safety by design and protective measures. This means that information for safety should be used after the manufacturer has determined that further risk reduction by making the medical device inherently safe and taking protective measures is not practicable. The text for information for safety can be prescribed by local regulations. The verification of the effectiveness of the information for safety can be performed by the usability engineering process. Information for safety needs to give the user clear instructions of what actions to take or to avoid a hazardous situation or harm from occurring. This is usually provided in the form of warnings or precautions. Information for safety can be given in the form of a warning label attached to medical devices or as a warning statement in the instructions for use. Some examples are given below:

- Warning: Do not step on surface.
- Warning: Do not remove cover, risk of electric shock.

- Warning: Use with caution.

Disclosure of Residual Risk Disclosure of residual risk is descriptive and can provide background on the residual risks involved in using the medical device. The aim is to disclose in the accompanying documents information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risks against the benefits of using the medical device. The manufacturer should consider means and media to disclose the residual risk. This information can be significant in the process of clinical decision-making. Within the framework of the intended use, the operator or the user can decide in which clinical settings the medical device can be used to achieve a certain benefit for the patient. The disclosure of the residual risk can also be useful for the operator, the user or the hospital organization to prepare the patient for possible side effects or hazards that can occur during or after the use of the medical device. Note that operator, user and patient can be the same person, for example, for medical devices used in the home healthcare environment. Some examples are given below to illustrate the residual risks associated with using the medical device and such side effects that are normally disclosed. The residual risks of radiation therapy for tumours can include the possibility of erythema or epilation. Patients undergo magnetic resonance imaging (MRI); they sometimes experience anxiety due to being in an enclosed space, hearing the loud noise generated by the equipment and needing to remain still during imaging.

Evaluation of Overall Residual Risk

After the assessment of every identified separate hazardous situation, the manufacturer then considers the combined impact of the individual residual risks and decides whether the overall residual risk meets or exceeds the criteria for residual risk acceptability stated in the risk management plan. This step is particularly important for complex medical systems and for medical devices with a large number of individual risks. The evaluation can be used for making a case that the product is safe. However, the determination of overall residual risk is a difficult and challenging task that cannot be achieved simply by numerically adding all individual risks. It is even uncertain if adding risks is possible at all, because each probability of occurrence of harm is related to a different severity of that harm. This difficulty also arises for the following reasons:

Even in the later stages of medical device development, confidence in the probability estimates can vary considerably. Some probabilities are known precisely either from history with similar medical devices or from testing. Other probabilities are only estimates and might be known very imprecisely or not at all, such as the probability of a software failure. Also, it is usually not possible to combine the severities of individual harms within the broad categories usually used in risk analysis. ISO 14971 does not specify that the criteria for risk acceptability for individual risks need to be the same as the criteria for overall risk acceptability. The criteria used to evaluate individual risks are usually based on the probability of occurrence of particular severities of harm.

The key to successful risk management in medical device design is to start early. As soon as conceptual designs are available, the risk management process can begin. A preliminary hazard analysis can be useful in selecting the concept with the highest level of inherent safety. Later, as the design is developed, design reviews at key points in the development process will allow changes to be made without significantly affecting the project schedule. The further along in the design process that changes are identified, the fewer choices are available to mitigate hazards without significant schedule implications.

Generally, risk management activities will identify opportunities to improve device performance. The benefits of conducting risk analysis during medical device design can be significant and can be used to offset some or all of the cost of implementing risk-mitigating measures. There is always a trade-off in how to manage risk. Hardware or software controls are generally viewed as more effective since they are more reliable than humans. However, since there is need for human interaction in the operation of all medical devices, the element of risk needs to be adequately evaluated. Minimizing the level of routine human intervention will reduce risk and improve efficiency. Such risk reduction must be weighed against the cost of automating tasks that can be performed by individuals.

References

1. ISO 14971: 2019 Medical devices – Application of risk management to medical devices ANSI/AAMI/2019.
2. ISO/TR 24971:2013 Medical devices – Guidance on the application of ISO 14971.

ISO 19227: Implants for Surgery – Cleanliness of Orthopedic Implants

Nandakumar Palani

1 Introduction

Medical implants are planted into a human body by surgery or naturally formed cavity and are planned to retain over short or longer period depending upon the type of surgery. FDA came up with standards to classify the devices which are placed in the human body regardless of the location and period also called as medical implants.

Implantable devices are partly human-made implants or natural implants which are fully introduced into the subject and planned to retain after the surgery for a period of time based on the need.

The cleanliness of the implants involves various steps and process based on the ISO 19227 Implants for Surgery – Cleanliness of Orthopaedic Implants.

Cleaning of orthopaedic implants is an important step in the process, and to achieve the cleanliness, biocompatibility and controlling the microbiological load are required for the sterilization process.

The application of the implants decides the constitutive material to manufacture the implant which should be safe and free from the contaminants that can be released from or reside on their surface. Cleanliness of orthopaedic implants is a key factor to ensure the biocompatibility of an implant. Cleaning is a needed step in the process to remove implant material contaminations coming from the manufacturing process. In cleaning materials should not react with constitutive materials and damage the biocompatibility or disable the performance of the implant. The cleaning agents should have proven the biocompatibility and does not damage or impair the implant performance.

N. Palani (✉)
R&D Engineer, Medical Devices, Milpitas, USA

M.Sc., Electronics, Chennai, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_4

Based on these requirements, the cleaning process validation and the biological evaluation of the implant are interconnected according to ISO 10993-1.

The cleaning process for orthopaedic implants can be sterile or non-sterile which is the manufacturer responsibility to provide implants clean from manufacturing contaminants.

The cleaning validation is to evaluate the cleaning process effectiveness in reducing contaminants in the form of physical, chemical and biological below a defined level. The evaluation and validation of cleaning methods is a critical task which requires in-depth knowledge of the manufacturing process on orthopaedic implants to identify contaminants and potential reactions with implant materials and chemical used in the cleaning process.

The effectiveness of the cleaning process is done during the manufacturing process in a separate environment as an alternative to final cleaning; the cleanliness of implants can be controlled by manufacturing in a clean environment and with clean processes.

The international ISO 19227:2018 "Implants for surgery—Cleanliness of orthopedic implants—General requirements" specifies requirements for the cleanliness of orthopaedic implants and test methods for the cleaning process validation.

Based on the standard ISO 19227:2018, the organized process for cleanliness of orthopaedic implants allows to reduce particles and chemical and biological contaminants below a defined level during manufacturing process. To make this happen, the implementation of the ISO 19227 standard, the manufacturer needs several steps to be set up:

- A review on the risk assessment on the cleaning process (development, validation and processing methods)
- A defined method development based on implant material characteristics, manufacturing steps/process and the implant performance
- A defined level of cleanliness requirements after final cleaning
- A cleaning methods validation for each implant
- A biological evaluation according to ISO 10993-1 and a validation of the sterilization process (Fig. 1)

Material and Methods and Results

2 General Requirements

2.1 Quality Management System

The set of methods or activities carried out for the implant cleanliness following this document shall be transferred to a formal quality management system.

The QMS which is widely used across all the countries for medical devices is ISO 13485.

Fig. 1 Physical, chemical and biological contaminants

2.2 Risk Management

Risk management is an iterative cycle which is done during the design, development and validation of the implant cleaning process and with continuing the implementation of cleaning methods.

The risk management process involves the implant cleaning process which is evaluated to achieve an accepted level of cleanliness, for example, controlled environment for cleaning and the manufacturing process.

The manufacturing process of an implant includes cleaning process and possible contaminants and its hazards, for example, the manufacturing steps are identified at each stage and based on which the design and validation of a manufactured implant involves cleaning process performed within a risk management system.

Hazards-related risks in cleaning are considered during the design of the cleaning process and when establishing design requirements for the critical cleaning process and the final cleaning step. Annexure A identifies some of the areas which cause possible contamination during the cleaning process and can be a harm.

Hazards-related risk assessment after the cleaning process shall be done once the designing of the cleaning process is completed and shall include characteristics of the implant material, manufacturing process before starting cleaning, characteristics involved in the cleaning process and, after implementing the final cleaning, the implant exposed to environment. Requirements for cleanliness shall be defined considering the contaminants which are intended to be removed by final cleaning step, and additionally contaminants are introduced by the cleaning process itself.

The following minimal questions shall be addressed during a risk assessment:

(i) What is the involvement of potential contaminants associated with the implants during the implant manufacturing process and implant cleaning process?

(ii) What are the risks involved in these contaminants during the manufacturing and cleaning process?
(iii) What are the potential interactions involved between the contaminant substances and the implant material?
(iv) What are the implant cleaning process involved in previous steps or other operations for removing these potential contaminants from the surface?
(v) What are the potential contaminants brought in by the implant cleaning process?

Risk assessment-based additional questions shall be addressed which are part of the manufacturing process:

(i) What are the test methods selected for the validation of the cleaning process able to assess the level of the potential contaminants on the implants, considering the limit and accuracy of the method?
(ii) What are the acceptance criteria for each cleaning step involved?
(iii) Following validation, what process control requirements are required to maintain cleanliness during manufacturing?
(iv) What are the process changes or improvements required in revalidating the product effective cleanliness?

Based on cleanliness acceptance criteria, cleaning validation can be performed.

2.3 Design of Cleaning Process

The in-process cleaning design requirements and the final cleaning shall be defined, based on the implant material characteristics, its intended performance and manufacturing process before cleaning, and also the hazards introduced by cleaning process are analysed (refer Annexure A). The cleaning processes shall be designed based on the cleanliness acceptance criteria of the implant material after final cleaning which are addressed.

The manufacturer and the cleaning subcontractor (if applicable) shall define the in-process cleanings which are critical based on the risk analysis of the manufacturing process and the in-process cleaning step during the final cleanliness of the implant. The risk assessment shall be used to determine level of severity and number of occurrences. Subsequent activities in the design, verification and validation of the implant manufacturing and cleaning processes (including inspection steps) should then concentrate on the development of control measures to mitigate these risks.

Even the drying operation which is performed at the end of the cleaning shall be considered to be part of the cleaning.

The cleaning process shall be designed in such a way to not degrade the biocompatibility and the intended performance of the implant.

The cleaning process shall be designed in order to limit contamination of the implant with cleaning agents, rinsing agents or contaminants coming from the cleaning process itself.

The cleaning process shall be able to decrease the contaminations coming from the previous manufacturing steps to an adequate predetermined level.

During final cleaning of implants, in order to prevent contamination of implants, a controlled environment or protection shall be implemented between final cleaning and packaging.

Note 1: Controlled environment does not necessarily mean the use of a clean room. While clean rooms are usually used for implants delivered sterile, this might not be the case for implants delivered non-sterile.

Note 2: ISO 14644 (all parts) contains information which might be useful, if clean rooms and associated controlled environments are used.

The cleaning facilities can be chosen by the manufacturer in order to simplify validation or verification activities of the cleaning process. The criteria for defining the cleaning families shall be justified and documented. In an implant represented by the worst-case specimen for a cleaning family, the manufacturer shall take the specification of cleanliness, the ability of the implant to be cleaned as well as the equivalence of the cleaning process of the worst-case specimen and the cleaning process of the implant.

2.4 Validation Process

The in-process cleaning and final cleaning process shall be validated in order to establish that the processes consistently yield implants complying with the cleanliness acceptance criteria defined for final cleaning.

Note 1: Cleaning processes and agents might influence the materials, surface properties, coatings or intended performance(s) of the implant.

Note 2: Guidance for validation of processes is given in IMDRF SG3-N99-10-2004.

The validation of the cleaning processes shall address the following (if applicable):

(a) *Types of contamination to be removed which is identified during the risk assessment*

(b) *Implant characteristics:*

1. *Implant materials*
2. *Implant size, shape and accessibility*

(c) *Cleaning steps:*

1. *Removing contaminations from the implant material with different cleaning agents*
2. *Removing cleaning agents with rinsing agents*
3. *Removing rinsing agents*

Validation shall be conducted on each implant. Validation shall comprise tests which demonstrate at relevant level of the process and even at the worst-case scenario the cleanliness requirements can be fulfilled. The process consistently produces implant meeting its cleanliness acceptance criteria.

Note 3: In some cases the relevant level of the process might be both the lower and upper, while in other cases only one of these levels might be relevant.

Note 4: ASTM F3127 provides guidance on cleaning process validation methods.

During the cleaning process, the worst-case specimen shall be used to conduct validation under the worst-case scenarios as determined by the manufacturer or cleaning subcontractor (if applicable). When determining the worst-case conditions, each cleaning steps like cleaning, rinsing and drying shall be taken into consideration. Based on the risk assessment, the manufacturer shall justify and document why any implant or test dummy is the worst case.

As a result of the risk assessment outcomes, there shall be changes made to the processing and manufacturing method like installations and/or parameters. The risk assessment shall determine if the cleaning process shall be revalidated and determine the extent of the revalidation. If the implant cleaning method and the cleanliness specifications or the worst-case specimen of a cleaning family is changed, the cleaning process shall be revalidated. Cleaning validation is interconnected with the biological evaluation and implant sterilization validation. Even if cleaning process validation gives a high result and level of confidence risks regarding cleaning is acceptable, the acceptability and validation of the cleaning design is only possible after implants undergo biological evaluation according to ISO 10993-1 and implant sterilization validation. If any new hazards are identified during this biological evaluation which can be mitigated by the cleaning process, the impact of these new hazards on cleanliness acceptance criteria and cleaning validation shall be reassessed. The manufacturer decides the order of cleaning validation, biological evaluation and implant sterilization validation. Cleaning validations are typically performed before or in parallel to biological evaluation and implant sterilization validation.

Note 5: A typical order for cleaning validation, biological evaluation and implant sterilization validation is given in Fig. 3.

Note 6: Cleanliness, microbiological contamination and biocompatibility of the implant might be influenced by the implant packaging.

2.5 Sampling Process

A sampling plan with an appropriate number of samples shall be established as part of the risk assessment of the cleaning process. When appropriate, sampling plans can be based upon statistically valid rationale for number of test specimens.

Each worst-case condition shall be tested when validating under worst-case conditions. At least three cleaning batches shall be tested when establishing the reproducibility of the process.

2.6 Manufacturing of Test Substances

In order to establish the conformity to the requirements of this document, tests shall be conducted on specimens manufactured, cleaned and packaged with methods and installations and in an environment representative of or more challenging than the manufacturing, cleaning and packaging process applied to the implant.

For the validation of critical in-process cleanings, packaging of specimens can be required between cleaning and testing of specimens, even if a packaging is not performed during the normal manufacturing at this stage. In this case, care shall be taken to ensure that the packaging does not influence the cleanliness of the specimens.

If a test (e.g. cytotoxicity) requires that specimens be sterilized, the sterilization method shall be that applied for terminal sterilization (for implants delivered sterile) or recommended for sterilization by the user (for implants delivered non-sterile).

The processing method, installations and parameters used for the manufacturing, cleaning, packaging and sterilization (if applicable) of the test specimens shall be documented.

2.7 Testing Methods and Efficiency

All the test methods used to demonstrate the conformity to the requirements of this document shall be validated and documented.

Note 1: Requirements for the competence of testing laboratories can be found in ISO/IEC 17025.

The following elements shall be documented, if applicable:

(a) *Justification of the test method(s) used according to the types of contaminant that can be present on the implant*

(b) *Extraction efficiency*

(c) *Detection limit, quantitation limit and accuracy of the method*

(d) *Extraction blanks and reference materials*

(e) *Adequacy to demonstrate the conformity to the predetermined acceptance criteria*

Note 2: Methods for the validation of analytical procedures can be found in ICH Q2(R1).

3 Cleanliness Evaluation: Test Methods and Cleanliness Acceptance Criteria After Final Cleaning

3.1 Detailed View

Test methods are to be considered when assessing the performance of each critical in-process cleaning and/or final cleaning. If adequately justified, some of the tests may be excluded based on the cleanliness requirements of the implant, the characteristics of the production and/or the cleaning process, the data gathered from previous cleaning processes and the data available from history.

Based on the type of contamination that can be present on the implant, other tests may be conducted. The preliminary cleanliness requirements shall be established by documenting the acceptance criteria for each test. Final cleanliness requirements shall be established after the results of the biological evaluation according to ISO 10993-1 and the results of the implant sterilization validation are available.

Note 1: For the relation between production and/or cleaning design, validation and risk management, see Fig. 2.

Note 2: For the relation between cleaning validation, biological evaluation and sterilization validation, see Fig. 3.

3.2 Visual Test

Acceptance criteria for visual inspection for visible contaminants remaining after cleaning shall be established by the manufacturer of the implant.

After cleaning, the implant being inspected shall comply with the manufacturer's acceptance criteria.

Note: EN 13018 is one method that can be used for acceptance criteria for visual inspection.

3.3 Bioburden Test

If the purpose of the cleaning process is to ensure that the bioburden is less than or equal to a predetermined level, the bioburden on the implant shall be determined as specified in ISO 11737-1.

Specimens shall not be sterilized.

The predetermined level shall be sufficiently low such that the sterilization method specified is adequate to achieve the desired sterility assurance level.

The results shall be less than or equal to the predetermined level.

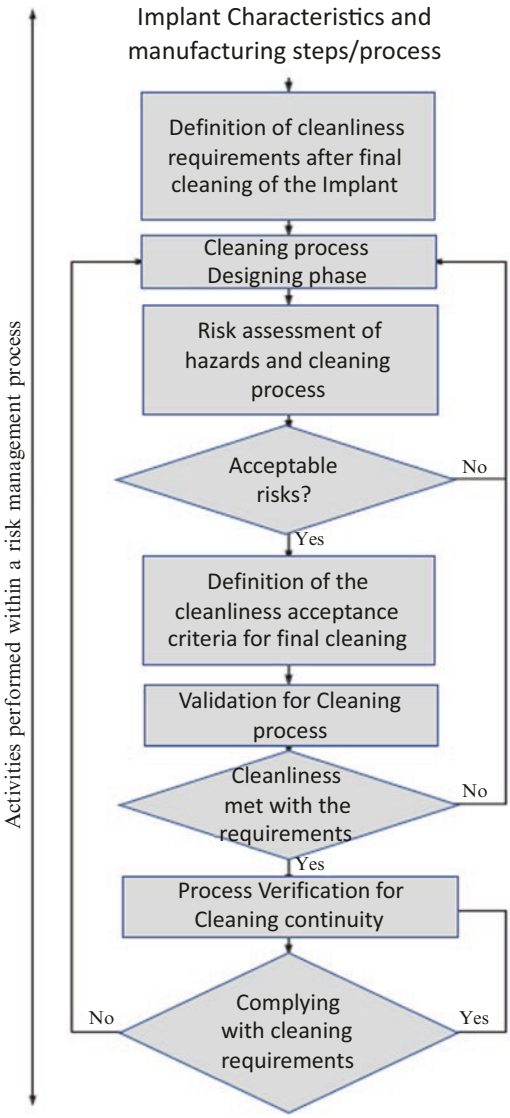


Fig. 2 The relation between cleaning design, validation and risk management

3.4 Bacterial Endotoxins

If the purpose of the cleaning process is to reduce the bacterial endotoxin contamination, then a validated test shall be conducted to measure the level of bacterial endotoxins.

If an endotoxin limulus amoebocyte lysate (LAL) test is used, it shall be conducted according to an established method described in a recognized pharmacopoeia after extraction from the implant with a validated method. The level of bacterial endotoxin per implant shall be not more than 20.0 endotoxin units.

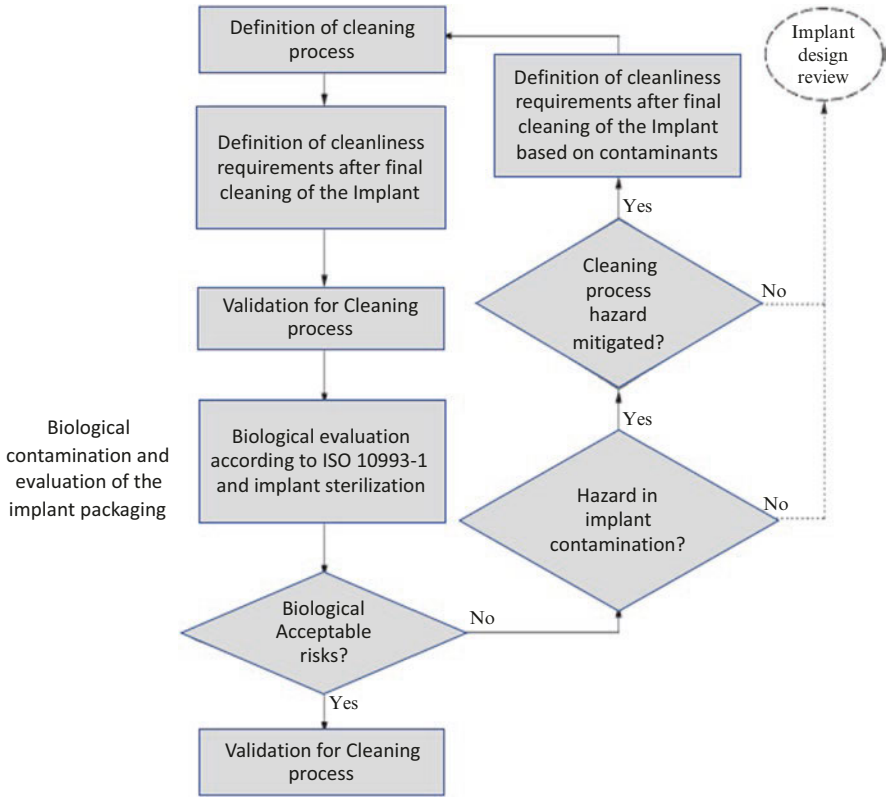


Fig. 3 Shows how cleaning validation, biological evaluation and sterilization validation are related

Note 1: Orthopaedic implants are not usually in contact with cerebrospinal fluid. In case of contact with cerebrospinal fluid, other limits can apply.

Note 2: AAMI ST72 gives helpful assistance for selection of test methods and acceptable levels of endotoxin contamination. It also gives helpful information on the effect of sterilization on endotoxin contamination.

Note 3: European Pharmacopoeia, Section 2.6.14, and USP, Section <85>, present appropriate methods for LAL testing.

3.5 Organic Contaminants

Detailed View

For chemical analysis of organic contaminants, a number of methods can be considered as common practice. Each method possesses advantages and disadvantages and might not detect all organic contaminants possible in the production of orthopaedic implants and/or introduced by the cleaning process.

Selection of the method(s) to be applied shall be based on, at least:

(a) Type of contamination that can be present on the implants
(b) Type of implant material(s)
(c) Sensitivity of the analytical method

The total organic carbon (TOC) method or another suitable method shall be used for detection of water-soluble organic contaminants.

The total hydrocarbons (THC) method or another suitable method shall be used for detection of hydrocarbons soluble in non-polar solvents, unless there is no risk of contamination with hydrocarbons.

Requirements for extraction and detection for the TOC and THC methods are described.

Note 1: Some implant intrinsic materials might release organic contaminants in the extraction solvent, and it might be necessary to implement adequate procedures to differentiate between intrinsic materials of the implant and contaminants.

The tests may be conducted on either sterilized or non-sterilized specimens.

Note 2: Sterilization can have an influence on type and number of organic contaminants resulting out of production and/or cleaning.

Biological evaluation data from devices with known organic contamination, manufactured with similar materials and manufacturing and cleaning processes, may be used to establish preliminary or, if appropriate, final acceptance levels for organic contaminants.

Note 3: TOC and THC methods are able to detect a large spectrum of organic contaminants without the possibility of identification of specific contaminants. For the TOC method, water is used for extraction, which results in reduced exhaustiveness with respect to non-polar contaminants. Both methods are useful to demonstrate, during the cleaning validation, that the process is under control. They do not intend to demonstrate that specific organic contaminants are non-toxic or are non-critical with respect to biological effects. If a company has no historical data on TOC or THC tests that can be related to a corresponding biological evaluation, the limits set forth in NF S94-091 (0,500 mg per implant for TOC and 0,500 mg per implant for THC) can serve as a starting point for acceptance levels. Specific organic contaminants can already be critical in concentrations significantly below the limits given by NF S94-091. Both type and amount of the single organic contaminants are relevant.

Note 4: One common approach is to first quantify the contamination. Subsequent identification of the contaminants can be helpful to understand the type of contamination (e.g. in case of untypically high contamination). However, the identification before quantification of contamination can be helpful to define allowable limits of contamination.

Extraction Method

Organic contamination shall be determined after exhaustive extraction from the implant using an appropriate solvent.

For water-soluble organic contaminants, water of sufficient purity not to interfere with the test method shall be used as a solvent.

For hydrocarbon contaminants, non-polar solvents are preferable for extraction and should be used. The solvent used for THC tests shall be chosen in order not to decompose the tested material and in order to avoid leaching from the material. If compatible with the material, hexane or halogenated solvents may be used. For example, for UHMWPE and PEEK implants propyl alcohol may also be used despite being a low-polar solvent.

Care shall be taken that the equipment to be used for extraction does not interfere with the solvent.

The extraction conditions shall be justified.

Note 1: Extraction methods can be found in ISO 10993-12, ASTM F2459 or ASTM G136.

The exhaustiveness of extraction shall be demonstrated.

Note 2: When the quantity extracted is below the quantification limit after the first extraction, it can be considered that exhaustiveness of extraction has been demonstrated.

The exhaustiveness of extraction conditions shall be verified on the worst-case specimen prior to finalizing testing on the cleaning family.

Detection Method

Detection including quantitation and/or identification of organic contamination as selected shall be performed by validated methods.

The TOC, if investigated, shall be determined in the extracts and shall be quantified using such methods as described in EN 1484, European Pharmacopoeia 2.2.44 or USP <643>.

The THC, if investigated, shall be determined in the extracts and shall be quantified using methods such as gas chromatography as described in ISO 9377-2, Fourier transform infrared spectroscopy (FTIR) as described in ASTM D7066-04 or another validated test method.

3.6 Inorganic Contaminants

The inorganic contaminants likely to be present on the implant shall be identified during the risk assessment as required.

The inorganic contaminants identified to be critical in the risk assessment shall be determined after exhaustive extraction from the implant using water, water supplemented with acid or another adequate solvent, if justified.

Care shall be taken that the equipment to be used for extraction does not interfere with the solvent.

The extraction conditions shall be justified.

Note 1: Extraction methods can be found in ISO 10993-12, ASTM F2459 or ASTM G136.

The exhaustiveness of extraction shall be demonstrated.

Note 2: When the quantity extracted is below the quantification limit after the first extraction, it can be considered that exhaustiveness of extraction has been demonstrated.

The exhaustiveness of extraction conditions shall be verified on the worst-case specimen prior to finalizing testing on the cleaning family.

Note 3: Some implant intrinsic materials might release inorganic contaminants in the extraction medium, and it might be necessary to implement adequate procedures to differentiate between intrinsic materials of the implant and contaminants.

After extraction, a suitable method shall be used in order to assess inorganic contaminants. Examples of suitable methods are:

(a) *Inductively coupled plasma in combination with atomic or optical emission spectrometry*

(b) *Inductively coupled plasma in combination with mass spectrometry*

(c) *Ionic chromatography*

(d) *Ionic chromatography in combination with mass spectrometry*

Note 4: If water is used for extraction, the conductivity of the extract can be used to indicate soluble ionic species contamination before using more specific test methods.

The inorganic contaminant acceptance levels shall be determined using the data on the biological effects of each inorganic contaminant.

Note 5: A possible method for determining allowable limits for inorganic contaminants is provided in ISO 10993-17. Acceptance criteria for elemental impurities can also be found in ICH Q3D.

3.7 Particulate Contamination

If the purpose is to demonstrate cleanliness regarding particulate contaminants, then corresponding investigations shall be conducted.

Selection of type and sensitivity of the test shall be performed based on the results of the risk management process. If extraction is conducted, care shall be

taken to avoid particles produced as a result of mechanical forces applied during the extraction process.

Note: AAMI TIR42 deals with the evaluation of particulates associated with vascular implants. However, AAMI TIR42:2010, Clause 8 and Annex A give helpful assistance for selection of acceptable levels and test methods of particulate contamination that could be applied to other types of implants.

3.8 Cytotoxicity

The cytotoxicity of the orthopaedic implant shall be determined using a method described in ISO 10993-5. The specimens shall be sterilized.

Any orthopaedic implant demonstrating a cytotoxic effect as defined in ISO 10993-5 shall be investigated to determine the cause of the cytotoxic effect. If this effect is related to contamination not removed by the cleaning process or to the cleaning process itself, control measures to mitigate this risk shall be implemented.

Note: Cytotoxicity is usually part of the biological evaluation of the implant as per ISO 10993-1. It is a useful in vitro test, sensitive to many types of contaminants, which can be used to assess the effectiveness of the cleaning process. However, even if a cytotoxic effect is observed, this might not be related to the cleaning process, and other root causes might have to be investigated.

4 Cleaning Validation

Guidance on setting the acceptance criteria and what types of residuals to look for in a cleaning validation, every manufacturer has a defined set of tests and acceptance criteria based on the regulations to screen for potential contaminants and residuals.

The tests allowed to be part of the manufacturing process are based on the risk and acceptance criteria of the device using the below steps:

- Risk analysis of the manufacturing process to identify most critical contaminants and residuals
- Selection of analytical tests that can detect targeted residuals
- Selection of a sampling strategy to get results based on the correct and meaningful set of data
- Development of acceptance criteria based on assessment of patient safety, historical data of device and patient, toxicological risk assessment or biocompatibility tests

The exact method to determine how clean enough the implant is has been a challenging measurement with the validation process. The acceptance criteria are set

based on the analytical results from measuring the cleanliness to those tests that provide an indication of device safety (like cytotoxicity testing). However, the difficulty with using a simple biocompatibility test to set acceptance criteria is that there are occasions where a device may be safe, but not clean, and occasions when a device may be clean, but not safe.

Cytotoxicity testing has commonly been used as an indicator that device cleanliness is acceptable, and because cytotoxicity testing is an extremely sensitive test, this does provide a good general indication of cleanliness. However, it should not be assumed that passing cytotoxicity equals safety. There is, after all, a whole suite of biocompatibility tests addressing biological risks outside of cytotoxicity that are necessary to support safety.

If passing a cleaning validation does not provide an indication of patient safety, and the analytical methods used for cleaning validations are not appropriate or sensitive enough for toxicological risk assessment, perhaps the previous ways of setting acceptance criteria for cleanliness are misguided.

Understanding that demonstrating device safety is a task separate from validating cleanliness, ISO 19227 prescribes a set of tests for demonstrating cleanliness along with acceptance criteria broadly applicable to orthopaedic implants. These tests and acceptance criteria (where specified) are outlined below:

- Visual test – acceptable when meeting specifications of the manufacturer
- Bioburden test – acceptable when the level of specified sterility assurance is met
- Bacterial endotoxin – acceptable when less than 20.0 endotoxin units
- Total organic carbon (TOC) – acceptable when less than 500 µg/device
- Total hydrocarbon content (THC) – acceptable when less than 500 µg/device
- Metals – acceptable when less than limits established by ICH Q3D or 10993-17
- Cytotoxicity – acceptable when passing per 10993-5

The most significant takeaways from ISO 19227 are the suggested acceptance criteria for common analytical tests that have, up to now, been difficult to interpret as they do not have the specificity and sensitivity to adequately indicate safety. Separating the ideas of safety from cleanliness helps to keep the determination of safety within the realm of biocompatibility per ISO 10993 and allows manufacturers to set common-sense acceptance criteria in situations where criteria based on biocompatibility do not make sense.

Ultimately, for cleanliness of final finished devices, the points of greatest value of a cleaning validation per ISO 19227 are to demonstrate control over processing, know the level of cleanliness at the time biocompatibility was established and then track cleanliness looking for unexpected changes using routine monitoring to know when biocompatibility might be in question.

5 Continued Process Verification (CPV)

To ensure the fulfillment of defined cleanliness requirements, a routine monitoring of the critical process parameters and/or process environment, according to documented procedures, shall be implemented.

Routine control testing of the cleaning processes shall be established as part of the quality management system to document the type and time interval for each periodic test.

The frequency for performing each test shall be determined considering the reproducibility of the process, the risks related to any contaminants as well as the frequency and volume of manufacture.

6 Documentation

All documents and records required to demonstrate conformity to this document shall be established and maintained in a manner consistent with the requirements of the manufacturer's quality management system.

Annexure A: (Informative) Potential Sources of Harm in a Cleaning Process

During the design of a cleaning process, at least the hazards relating to the following characteristics should be considered:

- Shape of implants and accessibility of its different surfaces
- Constitutive material(s) of the implant
- Contamination of the implant before cleaning
- Physical-chemical characteristics of the implant
- Cleaning techniques
- Materials coming into contact with implants
- Cleaning equipment, fixtures, baskets and control systems
- Maintenance methods and frequency
- Cleaning agent/compounds used
- Concentration of the cleaning agent
- Purity and potential toxicity of the liquid agents, especially for the last cleaning or rinsing steps
- Action of the cleaning agent on bacteria and fungi
- Action of the cleaning agent on physicochemical contamination
- Cleaning temperature
- Mechanical effects during cleaning (ultrasound, agitation and spraying)

- Position of implants during cleaning, rinsing and drying
- Load of the cleaning unit
- Cleaning time
- Renewing of the cleaning agent
- Succession of the cleaning and rinsing steps
- Rinsing agent used
- Rinsing temperature
- Mechanical effects during rinsing
- Renewing of the rinsing agent
- Rinsing time, flow and volume
- Drying method
- Drying temperature
- Drying time
- Aeration, HEPA filtration, air locks, cascading air pressurization

References

1. ISO 10993-12, Biological evaluation of medical devices—Part 12: Sample preparation and reference materials
2. ISO 10993-17, Biological evaluation of medical devices—Part 17: Establishment of allowable limits for leachable substances
3. ISO 14644 (all parts), Cleanrooms and associated controlled environments
4. ISO 14971, Medical devices—Application of risk management to medical devices
5. ASTM F3127, Standard guide for validating cleaning processes used during the manufacture of medical devices
6. NF S94-091, Implants for surgery—Validation requirements for cleaning process of orthopaedic implants before final packaging
7. IMDRF SG3/N99-10:2004, Quality Management Systems—Process Validation Guidance
8. European pharmacopeia 2.2.44, Total organic carbon in water for pharmaceutical use
9. European Pharmacopoeia 2.6.14, Bacterial endotoxins.
10. ISO 9377-2, Water quality—Determination of hydrocarbon oil index—Part 2: Method using solvent extraction and gas chromatography
11. ISO 10993-1, Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management system
12. ISO 10993-5, Biological evaluation of medical devices—Part 5: Tests for in vitro cytotoxicity
13. ISO 11737-1, Sterilization of medical devices—Microbiological methods—Part 1: Determination of a population of microorganisms on products
14. ASTM D7066-04, Standard Test Method for dimer/trimer of chlorotrifluoroethylene (S-316) Recoverable Oil and Grease and Nonpolar Material by Infrared Determination
15. BS_ISO_19227 Implants for Surgery—Cleanliness of orthopedic implants—General Requirements
16. ISO and IEC maintain terminological databases for use in standardization at the following addresses: IEC Electropedia: available at http://www.electropedia.org/; ISO Online browsing platform: available at https://www.iso.org/obp

ISO 21534: Non-active Surgical Implants – Joint Replacement Implants

Thamizharasan Sampath, Sandhiya Thamizharasan, and Prakash Srinivasan Timiri Shanmugam

Abbreviations

ANT	Anterior
KGy	Kilogray
NPL	National Physical Laboratory
POST	Posterior
UHMWPE	Ultrahigh-molecular-weight polyethylene

Highlights

- The chapter provides information on ISO and EU regulatory process involved in the joint replacement implants manufacturing process.
- It also explains the importance of material analysis in the design and development of non-active surgical implant devices.

1 Scope

This international standard specifies particular requirements for total and partial joint replacement implants, artificial ligaments and bone cement, hereafter referred to as implants. For the purposes of this international standard, artificial ligaments and their associated fixing devices are included in the term "implant". It specifies requirements for intended performance, design attributes, materials, design evaluation, manufacturing, sterilization, packaging and information to be supplied by the

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_5

manufacturer. The latest version of BS EN ISO 21534:2009 (Non-active surgical implants. Joint replacement implants. Particular requirements) was approved by CEN which is published on 31 October 2009. It is identical to ISO 21534:2007.

2 Normative References

The following referenced documents are indispensable for the application of this document.

ISO 4287: Geometrical Product Specifications (GPS) Profile method – Terms, definitions and surface texture parameters
ISO 7206-4: Partial and total hip joint prostheses – Determination of endurance properties of stemmed femoral components
ISO 7206-8: Partial and total hip joint prostheses – Methods of determining endurance performance of stemmed femoral components
ISO 14155-1: Clinical investigation of medical devices for human subjects – General requirements
ISO 14242-1: Wear of total hip-joint prostheses – Loading and displacement parameters for wear-testing machines and corresponding environmental conditions for test
ISO 14242-2: Wear of total hip-joint prostheses – Methods of measurement
ISO 14243-2: Wear of total knee-joint prostheses – Methods of measurement
ISO 14630-1: Non-active surgical implants – General requirements
ISO 14879-1: Total knee-joint prostheses – Determination of endurance properties of knee tibial trays

3 Terms and Definitions

Artificial ligament device: including its necessary fixing devices, intended to augment or replace the natural ligament
*Joint replacement implant***:** implantable device including ancillary implanted components and materials, intended to provide function similar to a natural joint and which is connected to the corresponding bones
Mean centre: position within the spherical head for which the average of the distances to a set of points uniformly distributed over the surface of the sphere is minimum
Radial separation value: difference between the mean radius of the spherical surface and the radius to the point on the spherical surface furthest from the mean centre

4 Intended Performance

For the purpose of this international standard, the intended performance of implants shall conform to Clause 4 of ISO 14630, and the design input shall additionally address the following matters:

- Intended minimum and maximum relative angular movement between the skeletal parts to which the joint replacement implant is attached
- Expected maximum load actions (forces and moments) to be transmitted to the bony parts to which the joint replacement implant is attached
- Dynamic response of the body to the shape/stiffness of the implants
- Expected wear of articulating surfaces
- Suitability of the dimensions and shape of the implant for the population for which it is intended
- Strength of the adhesion and durability of surface coatings or surface treatments
- The clinical indications and contra-indications for the use of a particular implant are complex and should be reviewed by the surgeons when they are selecting implants to be used for particular patients, relying upon their own personal judgment and experience. The lifetime of an implant depends on the interaction of various factors; some are the responsibility of the manufacturer, some, such as the implantation technique, are the responsibility of the surgeon in conducting the operation, and some relate to the patient, for example, the biological and physiological response to the implant, the medical condition of the patient, the conduct of the patient in respect of increasing body weight, carriage of heavy loads and adopting a high level of physical activity.

5 Design Attributes

The development of the design attributes to meet the performance intended by the manufacturer shall conform to the requirements of Clause 5 of ISO 14630, and in addition, account shall be taken of the following points:

- The strength of adhesion and durability of surface coatings and surface treatments
- The wear of the articulating and other surfaces
- Stability of the implant while allowing prescribed minimum and maximum relative movements between the skeletal parts
- Avoidance of cutting or abrading tissue during function other than insertion or removal
- The creep resistance and rupture characteristics, particularly as they relate to ligaments

Methods of assessment of the wear of articulating and other surfaces are prescribed in ISO 14242 and ISO 14243 (Table 1).

Table 1 Surface finish of metallic or ceramic partial implants

Articulating surfaces of metallic or ceramic components	Surface roughness value	Radial separation value
Total joint replacement	>0, 1 μm	
Partial joint replacement	>0, 5 μm	
Convex spherically total joint replacement	>0, 05 μm	>10 μm
Spherically partial joint replacement	>0, 5 μm	>100 μm
Concave spherically total joint replacement	>2 μm	>200 μm

6 Materials

ISO 14630 states that the acceptability of materials may be demonstrated by selection from the materials found suitable by proven clinical use in similar applications; for the purposes of this international standard, proven use should be demonstrated by records of implantation of at least 500 of the implants and recorded satisfactory clinical use over a period of not less than 5 years. The list of international standards for materials found acceptable through proven use for the manufacture of implants or for use in association with implants is given below (Table 2).

For the articulating surfaces of joint replacement implants, the following combinations of the materials are listed below. They have been found to be acceptable in particular applications provided adequate attention is given to design, surface finish and surface treatment (Table 3).

Dissimilar Metals or Alloys

For applications in which two dissimilar metals or alloys or the same metals or alloys in different metallurgical states are in contact where articulation is not intended, combinations used shall not produce unacceptable galvanic effects. For applications where one metal or alloy is in contact with another and articulation is not intended, the following metallic combinations involving the metals listed in Table 1 have been found to be acceptable and can be used provided adequate attention is given to design, surface finish, surface treatment and metallurgical conditions. The international standards for acceptable and unacceptable metallic combinations for use in non-articulating bearing surfaces of implants are listed below (Table 4).

7 Design Evaluation

Joint replacement implants shall be evaluated in order to demonstrate that the intended performance is achieved. This evaluation shall be in accordance with Clause 7 of ISO 14630 together with the particular requirements. This evaluation shall be undertaken using components fully representative of the final condition ready for implantation.

Table 2 Materials used in joint replacement implants

International standard for materials	Acceptable material for the manufacture of implants
ISO 5832	Wrought stainless steel, unalloyed titanium, wrought titanium 6-aluminium 4-vanadium alloy, cobalt-chromium-molybdenum casting alloy, wrought cobalt-chromium-tungsten-nickel alloy, wrought cobalt-nickel-chromium-molybdenum alloy, forgeable and cold-formed cobalt-chromium nickel-molybdenum-iron alloy, wrought cobalt-nickel-chromium molybdenum-tungsten-iron alloy, wrought high nitrogen stainless steel, wrought titanium 6-aluminium 7-niobium alloy, wrought cobalt-chromium-molybdenum alloy
ISO 5833	Acrylic resin cements
ISO 5834	Ultrahigh-molecular-weight polyethylene (powder and moulded forms)
ISO 6474	Ceramic materials based on high purity alumina
ISO 13356	Ceramic materials based on yttria-stabilized tetragonal zirconia (Y-TZP), ceramic hydroxyapatite
ISO 13779	Coatings of hydroxyapatite

Table 3 List of international standards for materials found acceptable or not acceptable for articulating surfaces of implants

Suitable material combinations for articulating surfaces	Unsuitable combinations of materials for articulating surfaces
(a) Wrought stainless steel/UHMWPE (b) Wrought high nitrogen stainless steel/UHMWPE (c) Cobalt-chromium-molybdenum casting alloy/UHMWPE (d) Wrought cobalt-chromium tungsten-nickel alloy/UHMWPE (e) Forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy/UHMWPE (f) Wrought cobalt-nickel-chromium-molybdenum-tungsten-iron alloy/UHMWPE, wrought titanium 6-aluminium 4-vanadium alloy 2/UHMWPE (g) Wrought titanium 6-aluminium 7-niobium alloy/UHMWPE (h) Ceramic materials based on alumina 2/UHMWPE (i) Ceramic materials based on zirconia/UHMWPE (j) Ceramic materials based on alumina/ceramic materials based on alumina (k) Forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy/forgeable and cold-formed cobalt-chromium-nickel-molybdenum-iron alloy (l) Wrought cobalt-chromium-molybdenum alloy/cobalt-chromium-molybdenum casting alloy (m) Wrought cobalt-nickel-chromium-molybdenum alloy/UHMWPE (n) Wrought cobalt-chromium-molybdenum alloy/UHMWPE	(a) Stainless steel/titanium-based alloy (b) Stainless steel/stainless steel (c) Stainless steel/unalloyed titanium (d) Stainless steel/cobalt-based alloys (e) Unalloyed titanium/unalloyed titanium (f) Unalloyed titanium/titanium-based alloys (g) Unalloyed titanium/cobalt-based alloys (h) Unalloyed titanium/UHMWPE (i) Titanium-based alloys/cobalt-based alloys

Table 4 List of materials found acceptable or non-acceptable for metallic combinations for non-articulating contacting surfaces of implants

Suitable combinations of dissimilar metals for non-articulating contacting surfaces	Non-acceptable metallic combinations for non-articulating contacting surfaces
(a) Cobalt-based alloys/titanium-based alloys (b) Cobalt-based alloys/other cobalt-based alloys (c) Stainless steel/titanium-based alloys (d) Stainless steel/stainless steel (e) Stainless steel/cobalt-based alloys	(a) Stainless steel/cobalt-based alloys (b) Stainless steel/unalloyed titanium

Preclinical evaluation shall consider:

- Biocompatibility of any materials not previously used.
- Mechanical loads and the related movements to which the implants can be subjected when functioning as prescribed by ISO 14630.
- Fatigue testing of highly stressed parts in accordance with ISO 7206-4, ISO 7206-8 and ISO 14879-1.
- Wear testing of articulating bearing surfaces in accordance with, e.g. ISO 14242-1, ISO 14242-2 and ISO 14243-1.
- The suitability of the dimensions and shape of the implant for the intended population. The suitability of the dimensions and shape of the implant for the intended population can be demonstrated by cadaver implantation; the use of imaging systems such as X-ray, CAT scan or magnetic resonance imaging; or reference to corresponding implants of proven clinical use.
- Adhesion and durability of coatings if present.

Surface roughness measurement: Surface roughness shall be measured according to one of the methods given in ISO 4287.

Sphericity measurement: Radial separation values for sphericity shall be measured according to a method demonstrated to be accurate and repeatable. A suitable method is described in the NPL.

Clinical investigation: The clinical investigation shall be conducted according to the general requirements of ISO 14155-1.

Post-market surveillance: The post-market performance of joint replacement implants shall be determined. Suitable methodologies include survival analysis (with revision as the endpoint) and clinical assessment. Where it is available, relevant information from joint replacement registries are taken into account.

8 Manufacture and Inspection

Metal Surfaces

All polishing operations on metallic components shall be performed using an iron-free material. Clean, degrease, rinse and dry all components and examine the

articulating surfaces using normal or corrected vision. The surfaces shall be free of any imperfections that would impair their function and also be free from deposited finishing materials or other contaminants. Examples of imperfections which might impair function include scale, tool marks, nicks, scratches, cracks, cavities, burrs and other defects.

Plastic Surfaces

Articulating surfaces of plastic components shall not be prepared using non-removable abrasive or polishing compounds. Clean, degrease (if necessary), rinse and dry the components and examine them using normal or corrected vision. The surfaces shall be free from particulate contamination.

Ceramic Surfaces

Ceramic components shall be cleaned, degreased, rinsed, dried and examined using normal or corrected vision. The articulating surfaces shall be free of any imperfections that would impair their function. Examples of imperfections which might impair function include particulate contamination, chemical discolouration (spots or larger areas), tool marks, nicks, chips, cavities and cracks.

9 Sterilization

The effects of the sterilization process shall not impair the intended performance of the implant. Implants containing UHMWPE and sterilized by ionizing radiation shall not be supplied for clinical use if an accumulated dose of radiation higher than 40 kGy has been received. This requirement does not apply if radiation intended to improve the mechanical characteristics of the material is combined with the radiation for sterilization purposes. The manufacturer shall conduct an investigation, and record the results, to ascertain the expiry date to be marked on the labelling for the implant.

10 Packaging and Information Supplied by the Manufacturer

Labelling of Implants

Labelling for implants designed for use on one side of the body only shall bear the symbol “LEFT”’ or “L” for implants to be used on the left side or “RIGHT” or “R” for implants to be used on the right side.

Table 5 Labelling of implants for use with or without bone cement

Implants usage	Primary legend	Alternative legend
Implants intended to be used with bone cement	*For use with cement*	*Cemented*
Implants intended to be used without bone cement	*Uncemented*	*Cementless*
Implants intended to be used optionally	*Use with cement or uncemented*	*No legend*

Instructions for Orientation of Implants

The instruction leaflet and/or manual shall, where necessary, indicate the required orientation of the implant relative to the body part. It shall also refer to the relevant marking(s) on the implant or the label.

Markings for Orientation of the Implants

The implant shall bear the symbol "ANT" on the front and/or "POST" on the back where this is necessary for interpretation of the instructions relating to the required orientation of the implant relative to the body given in the instruction leaflet and/or manual.

Placing of Markings on Implants

Markings shall be placed on the implant where they will not impair its intended function.

Restrictions on Use

If an implant is intended for a restricted population, this shall be stated in the instructions for use or in the manual.

Re-sterilization of Zirconia Ceramics

Components manufactured from zirconia ceramics shall include an instruction advising users "Do not sterilize using moist heat".

Labelling for implants shall bear an appropriate legend as shown in Table 5.

Reference

1. EN ISO 21534:2009 – Non-active surgical implants – Joint replacement implants. CEN, 31.09.2009.

ISO 16061: Instrumentation for Use in Association with Non-active Surgical Implants—General Requirements

Karnika Singh

1 Introduction

ISO 16061 lays out the general requirements for instruments that are used in cooperation with "non-active surgical implants". These requirements are applied to instruments during the time of manufacturing and refurbishment. This ISO is also applicable to power-driven instruments, but not to the power source itself. The safety requirements included in this ISO are associated with intended performance of the device, design, material, manufacturing, sterilization, packaging, and information provided by the manufacturer. ISO 16061 does not apply to instruments related to dental implants, transendodontic and transradicular implants, and ophthalmic implants. The ISO 16061:2015 is the latest version of this ISO.

2 Terms and Definitions

2.1 Associated Implant

It is a non-active surgical implant that is used along with the intended instrument during a surgical procedure.

K. Singh (✉)
The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_6

2.2 Instrument

It is a non-active medical device associated with a respective non-active surgical implant that is utilized during surgical procedures.

2.3 Resupplied Instrument

This refers to instrument or set of instruments that were returned to the manufacturer and have been issued again.

3 Intended Performance

The "intended performance" of an instrument would be defined with the following things in mind, in terms of safety, and documented as well:

(i) Functional characteristics
(ii) Intended circumstances for use

The published standards, published clinical and scientific literature, and validated test results should be taken into account. Also the extent to which the intended performance of the instrument was reached would also be determined.

4 Design Attributes

The design attributes of an instrument would be evolved keeping in mind its intended performance as defined by the manufacturer. The following things should be taken into account while deciding the design attributes:

1. Physical, mechanical, and chemical properties of the materials used in the instrument
2. Contamination levels of microbiological and particulate materials
3. Ease of use, cleaning, and maintenance
4. Expected degradation of the material characteristics because of sterilization and storage
5. Impact of contact between the instrument and body, the implant, and other instruments
6. Shape and dimensions of the instrument itself, along with their desirable effects on the body
7. Wear properties of materials and its consequences on the instrument itself and its body

8. Insertion, removal, and interconnection of parts
9. Degree of fluid leakage and/or diffusion of materials into and out of instruments
10. Efficiency and stability of instruments intended for measurement
11. Capability of the instrument or part of instrument that would be located by means of an external imaging device
12. Compatibility with any medicinal element incorporated put into or used with the instrument

5 Selection of Materials

The materials to be used in the instrument shall be chosen with reference to the properties to be incorporated in the instrument so that it serves the intended purpose. The following things should be taken into consideration: effects of manufacturing, handling, sterilization, and storage along with any treatment (chemical, electrochemical, thermal, mechanical, etc.) put on the surface or some surface of the instrument for modifying its properties. Potential reactions of instrument materials that may happen with human tissues and body fluids should be taken into account. The relevance of a given material for a particular application will be determined by:

(i) Documented evaluation in accordance with ISO 109993-1.
(ii) Choosing from the materials found suitable by proven clinical use in related applications. The list of some materials can be found in Annex A attached with the original ISO 16061 document.

6 Design Evaluation

6.1 General

Instruments would be evaluated along with the implant they are designed for so that it can be demonstrated that the intended purpose of the instrument has been realized. For safety demonstration, preclinical evaluation and risk analysis would be done according to ISO 14971.

6.2 Preclinical Evaluation

If preclinical evaluation is needed, the testing conditions would be similar to those of intended use.

6.3 Clinical Evaluation

The required clinical evaluation would be placed on the following:

(i) Critical assessment of appropriate scientific and clinical literature related to safety, performance, design characteristics, and intended use of the instrument or established similar instruments
(ii) Critical assessment of all the results obtained from all clinical investigations conducted with the associated implant under the intended conditions for use
(iii) Association of the clinical data provided in (i) and (ii) above

Whenever a clinical study is performed, it will be managed according to ISO 14155.

7 Manufacture

Instruments will be manufactured according to specifications of the required design attributes.

8 Sterilization

8.1 Products Supplied Sterile

In order for an instrument to be labelled "STERILE" (terminally sterilized instrument), the probability of the presence of a viable microorganism on the instrument has to be equal or less than $1 \text{ X } 10^{-6}$ at least in theory. Manufacturers are allowed to use other sterility assurance levels, as long as it is supported by a documented risk assessment. The ethylene oxide sterilization would be done in accordance with ISO 11135. The sterilization by irradiation would be done according to ISO 11137-1, ISO 11137-2, and ISO 11137-3. If sterilization were to be done by moist heat, it would be done according to ISO 17665-1.

8.2 Products Provided Non-sterile

For such instruments the manufacturer has to specify at least one relevant sterilization method that does not negatively affect the functional safety of the product. The restriction of no multiple sterilizations shall be informed. For the instruments that are marked non-sterile or declared to have the ability to be sterilized again, the manufacturer will provide information about handling such instruments according to ISO 17664.

9 Packaging

9.1 Protection from Damage in Storage and Transport

The packaging has to be custom designed for each instrument for conditions specified by the manufacturer for storage, transport, and handling (including temperature control, humidity, and ambient pressure, if applicable). The packaging has to ensure that it will protect the instrument against damage and deterioration but at the same time does not unfavourably affect the intended performance of the instrument.

9.2 Maintenance of Sterility in Transit

The instruments that are labelled "STERILE" would be packaged in a way that they stay sterile under normal storage, transport, and handling conditions with the exception of damaged protective packaging or opened. The packaging has to comply with ISO 11607-1 and ISO 11607-2.

10 Information Supplied by the Manufacturer

10.1 General

Any information that is supplied by the manufacturer intended for direct visual recognition should be easy to read under illumination of 215 lx by normal vision, corrected vision if applicable, from a distance that includes the form and size of the individual instrument. If the space were limiting on the instrument's individual packaging, the appropriate information would be given on an insert, accompanying document, or on the next coating of packaging, as relevant. The markings on small or specialized instruments that are not visible by the eye need to be made recognizable by using electronic methods, etc. Wherever relevant, symbols, abbreviations, and identification colour can be used in the labelling and accompanying documents of the instruments. All these elements (symbols, abbreviations, colours, etc.) should comply with ISO 15223-1. If there are no standards available for such usage, then manufacturer would describe each entity used, in the supplied documentation. All the information supplied by the manufacturer has to be clear such that it is not confused with other important information. It should be understandable to the intended user or people in general.

All units of measurement shall be indicated in SI units according to ISO 80000-1. Comparable units can be stated in parenthesis. The safety information of the instrument should be put on the instrument itself as far as possible. It can also be put on individual packaging or sales packaging if required. If neither of the above options

is feasible, this information should be supplied in the leaflet accompanying each instrument or unit. Wherever relevant, the instruments containing user adjustable control would clearly specify the function of each control. All the detachable components that are intended for usage separately from the original instrument would be identified by their batch code or by other relevant method. The format of any date would be YYYY-MM-DD, or YYYY-MM, or YYYY, complying with ISO 8601.

11 Labeling

The label should contain the following information:

(i) If the package holds any radioactive substance, it should have the appropriate marking specifying the type and activity of the radioactive substance.

(ii) Name and address of the manufacturer, comprising the city and the country at least.

Description of the instrument, its model designation, if possible, the batch number/serial number of the instrument followed by a relevant identification, for example, "LOT", "SN", or the lot, or serial number symbols ISO 7000-2492 and ISO 7000-2498, respectively. See ISO 15223-1:2012, 5.14 and 5.16.

(iii) A clear statement describing the intended purpose of the instrument so that it is not at all unclear to the user.

(iv) In the case of a terminally sterilized instrument, the contents that are sterilized should be indicated along with the method of sterilization, for example, the word "STERILE" or the sterile symbol ISO 7000-2499, or one of the "sterilized using…" symbols ISO 7000-2500, ISO 7000-2501, ISO 7000-2502, and ISO 7000-2503. See ISO 15223-1:2012, 5.20 or 5.21, 5.22, 5.23, and 5.24.

(v) If two identical or similar instruments are sold as both sterile and non-sterile, it has to be clearly indicated on the contents of particular package if they are non-sterile, wherever appropriate, for example, the "non-sterile" symbol ISO 7000-2609. See ISO 15223-1:2012, 5.26.

(vi) The "use by date" should be expressed as year and month, for example, the "use by date" symbol ISO 7000-2607. See ISO 15223-1:2012, 5.12.

(vii) It should be clearly indicated when the instrument is intended only for a single use, for example, the "do not reuse" symbol ISO 7000-1051. See ISO 15223-1:2012, 5.2.

(viii) Indicate any specific storage and/or handling conditions.

(ix) Specific operating instructions.

(x) Any warnings or precautions associated with the usage.

12 Instructions for Use

The instructions for use should contain the following information wherever relevant:

(i) The presence of any radioactive substance in the package along with its type and activity.
(ii) Contact details of the manufacturer with the city, country, and telephone number.
(iii) Instrument description and its model designation.
(iv) The intended purpose of the instrument should be clearly specified.
(v) The intended performance discussed in clause 4 and any relevant side effects.
(vi) Enough information to allow the user to choose a suitable instrument for themselves. Such information should include the instrument size, its accessories, related devices, etc. so that the user can get a safe combination.
(vii) If the instrument is terminally sterile, it should be indicated on the contents of the package along with the method of sterilization, for example, the word "STERILE" or the sterile symbol ISO 7000-2499, or one of the "sterilized using…" symbols ISO 7000-2500, ISO 7000-2501, ISO 7000-2502, and ISO 7000-2503. See ISO 15223-1:2012, 5.20 or 5.21, 5.22, 5.23, and 5.24.
(viii) If similar or identical instrument is sold in both sterile and non-sterile conditions, it should be accompanied by a set of instructions for sterilizing the contents of the instrument.
(ix) Instructions for the process of sterilization with appropriate cycle parameters for the non-sterile instrument or for handling the contents of a sterile package that got non-sterile due to opening of the package or damage. Maximum number of permitted re-sterilizing cycles should be specified.
(x) If the instrument is proposed to be reused, method of appropriate processing before reuse involving cleaning, disinfection, if relevant the process of sterilization with applicable cycle parameters and restrictions for the number of reuses, if any.
(xi) Clear indication stating the intent of instrument as "single use", for example, the "do not reuse" symbol ISO 7000-1051. See ISO 15223-1:2012, 5.2.
(xii) Particulars of any treatment of handling required before the instrument can be used, for example, final assembly, cleaning, sterilization, etc.
(xiii) Any specific storage and/or handling conditions.
(xiv) Warnings or precautions concerned with use, containing limitations on chemicals (e.g. alcohol) or other environmental conditions to which the instrument may get rationally exposed to during the clinical setting.
(xv) It should be expressed on the instrument if the whole instrument or any of its fragments can be detected externally by an imaging device along with the kind of device for this purpose.
(xvi) Instructions for legitimate disposal of the instrument and any specific or odd risks should be pointed out.
(xvii) Information about any medicinal products incorporated into or used with the instrument should be given wherever relevant.

(xviii) Date of issue or the latest revision of the instructions of use should be indicated if needed.

13 Instruments with Measuring Function

The limits of accuracy of such instruments should be indicated by a mark or on the label on the instrument as well as in the instructions for use. The gauges used for component size selection and *go/no-go* decisions are exempt from this requirement.

14 Restrictions in Combinations

If the instrument is designed for use in combination with other instruments, devices, or equipment, any limitations in the use of the combinations should be written on the label or in the user instructions.

15 Marking on Instruments

Instruments should be marked with the following entities:

(i) Manufacturer's name or trademark
(ii) Batch code or serial number, wherever relevant
(iii) Catalogue/article number, if relevant, and/or size implication, if required for safe selection or use

If the markings on the instrument would affect its performance or that there is not enough space to mark the instrument because of its small size, the instrument label shall supply all the required information.

16 Instruments Intended for Single Use

For instruments that are intended for single use, the user instructions would contain the information about the recognized characteristics and technical factors noted to the manufacturer that could offer a risk if the instrument is reused.

Reference

ISO 16061:2015(E) Instrumentation for use in association with non-active surgical implants—General requirements

ISO 22442: Medical Devices Utilizing Animal Tissues and Their Derivatives

Thamizharasan Sampath, Sandhiya Thamizharasan, Krithaksha V., and Prakash Srinivasan Timiri Shanmugam

Abbreviations

AAMI	Association for the Advancement of Medical Instrumentation
BSE	Bovine spongiform encephalopathy
CDC	Centers for Disease Control and Prevention
CJD	Creutzfeldt-Jakob disease
CPMP	Certified Project Management Professional
GMP	Good manufacturing processes
ISO	International Organization for Standardization
NaOH	Sodium hydroxide
PrPTSE	Prion protein associated transmissible spongiform encephalopathy
PRNP	Prion protein
TSE	Transmissible spongiform encephalopathy
WHO	World Health Organization
OIE	World Organisation for Animal Health

Highlights

- This chapter covers requirements and guidance for the evaluation of medical devices manufactured utilizing animal tissues or derivatives.

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

Krithaksha V.
RMKSSS, RMK Group of Institutions, Chennai, Tamil Nadu, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_7

- This chapter provides detailed information on validation and elimination of transmissible spongiform encephalopathy agent.

1 Part 1: Application of Risk Management

1.1 Scope

This part of ISO 22442 applies to medical devices other than in vitro diagnostic medical devices manufactured utilizing materials of animal origin, which are non-viable or have been rendered non-viable. It specifies, in conjunction with ISO 14971, a procedure to identify the hazards and hazardous situations associated with such devices, to estimate and evaluate the resulting risks, to control these risks and to monitor the effectiveness of that control. Furthermore, it outlines the decision process for the residual risk acceptability, taking into account the balance of residual risk, as defined in ISO 14971, and expected medical benefit as compared to available alternatives. This part of ISO 22442 is intended to provide requirements and guidance on risk management related to the hazards typical of medical devices manufactured utilizing animal tissues or derivatives such as (a) contamination by bacteria, moulds or yeasts; (b) contamination by viruses; (c) contamination by agents causing transmissible spongiform encephalopathies (TSEs); and (d) material responsible for undesired pyrogenic, immunological or toxicological reactions. For parasites and other unclassified pathogenic entities, similar principles can apply. The text of ISO 22442-1:2015 has been approved by CEN as EN ISO 22442-1:2015 without any modification. This second edition cancels and replaces the first edition (ISO 22442-1:2007), of which it constitutes a minor revision.

1.2 Terms and Definitions

Animal: any vertebrate or invertebrate [including amphibian, arthropod (e.g. crustacean), bird, coral, fish, reptile, mollusc and mammal] excluding humans (*Homo sapiens*)

Cell: smallest organized unit of any living form which is capable of independent existence and of replacement of its own substance in a suitable environment

Derivative: substance obtained from an animal material by a manufacturing process, for example, hyaluronic acid, collagen, gelatine, monoclonal antibodies, chitosan, albumin

Elimination: removal process by which the number of transmissible agents is reduced

Inactivation: process by which the ability to cause infection or pathogenic reaction by a transmissible agent is reduced

Medical device: any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s):

- Diagnosis, prevention, monitoring, treatment or alleviation of disease
- Diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury
- Investigation, replacement, modification or support of the anatomy or of a physiological process
- Supporting or sustaining life
- Control of conception
- Disinfection of medical devices
- Providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function

Non-viable: having no potential for metabolism or multiplication

Technical agreement: binding contract between two or more parties that assigns responsibilities for technical requirements

Tissue: organization of cells and/or extracellular constituents

Transmissible agents: bacteria, mould, yeast, parasites, viruses, TSE agents and unclassified pathogenic entities

1.3 Risk Management Process

Device Contact with the Patient

The quantity of material, the contact surface area and the type(s) of the material coming into contact with body tissues or fluids as well as the type of body tissue or fluid it comes into contact with shall be addressed in the risk analysis. Medical devices such as orthopaedic shoes or components such as leather straps that come into contact only with intact skin represent a low infective risk. The quantity of material coming into contact is one of the factors in producing biological effects. The structure of animal tissues being processed can affect the inactivation and/or elimination of transmissible agents, and the potential for retaining viable cells can be affected by the structure of the animal tissues and derivatives being processed.

Material Incorporated in the Medical Device

The following factors shall be addressed, if applicable:

(a) If viable, animal materials are utilized in the manufacture of the medical device, verification that the final medical device contains no viable animal material.
(b) The intended use of any animal tissue or derivative.
(c) Geographical source, species, age and feeding (including animal-derived protein) of animals.
(d) Veterinary control, conditions under which the animal materials are recovered, potential for cross-contamination.
(e) The type and anatomical source of tissue.
(f) The production process, particularly if it uses materials pooled from more than one animal.
(g) The nature of material utilized in the medical device (e.g. intact tissue).
(h) The method of utilization or incorporation into the medical device. In the case of medical devices utilizing several relevant constituents (e.g. from various species, origin or tissues) or several similar types of constituents produced using different methods, each individual constituent should be analysed separately.

Device Material Sterility and Other Microbiological Controls

Given the biological nature of animal tissues or derivatives, variations in the bioburden of bacteria, mould and yeast of the animal material shall be estimated.

Unwanted Outputs of Substances

The possible presence of toxic residue related to the manufacturing process utilized or degradation by-products shall be addressed taking into account the physical characteristics (e.g. porosity, heterogeneity) and chemical composition of animal tissues or derivatives.

Identification of Hazards and Hazardous Situations

The possible hazards associated with animal tissues or derivatives shall be identified and documented. Particular attention shall be applied to possible hazards posed by animal tissues or derivatives with regard to:

– Potential contamination by transmissible agents and their susceptibility to elimination and/or inactivation during processing
– Potential for contaminants on the finished material which can cause an undesired pyrogenic, immunological or toxicological reaction
– Potential for the finished material itself to cause an undesired pyrogenic, immunological or toxicological reaction

1.4 Risk Evaluation and Risk Control

In accordance with ISO 14971, all identified risks shall be evaluated. Biological safety shall be evaluated in accordance with ISO 10993-1. Risk evaluation for transmissible agents shall be implemented by separately addressing the risks related to different categories of transmissible agents. Annex B identifies the main categories of risk that should be considered. Regarding the TSE risk, compliance with requirements specified in Annex C for certain animal materials can indicate risk acceptability. Annex C combines elements of risk evaluation and risk control.

Risk Control for Viruses and TSE Agents

Risk control shall be implemented by separately addressing the risks related to different categories of viruses and TSE agents. After defining the characteristics of the product, the medical device manufacturer shall comply with the relevant requirements of both ISO 22442-2 and ISO 22442-3, except where either the animal species is such that manufacturers cannot fully meet the requirements of ISO 22442-2 or an inactivation process in accordance with ISO 22442-3 would cause unacceptable degradation. Tallow derivatives, animal charcoal and amino acids that are acceptable for TSE risk as discussed in Annex C, due to their processing and not their sourcing, shall also be considered to have acceptable risk regarding viruses. Regarding TSE risk, risk control measures specified in Annex C for certain animal materials shall be applied where relevant. If the manufacturer considers any requirement not to be relevant, the rationale and justification shall be documented. For medical devices where an inactivation process causes unacceptable degradation, manufacturers may rely on ISO 22442-2 in order to meet the requirements of this part of ISO 22442. If the animal species is such that manufacturers cannot fully meet the requirements of ISO 22442-2, they shall demonstrate that the level of inactivation of transmissible agents in a validated manufacturing process, as required in ISO 22442-3, is sufficient to achieve an acceptable level of risk.

Risk Control of Other Hazards

Risk control related to bacteria, moulds and yeasts, as well as undesired pyrogenic, immunological and toxicological reactions shall be implemented according to available standards. Tallow derivatives, animal charcoal and amino acids that are acceptable for TSE risk as discussed in Annex C, due to their processing and not their sourcing, shall also be considered to have acceptable risk regarding bacteria, moulds and yeasts, subject to maintenance of proper storage conditions. The manufacturer shall conduct periodic microbiological studies to identify and quantify the initial bioburden of the incoming animal material for the production of the medical device.

Residual Risk Evaluation

The TSE risk may be judged acceptable if the following criteria are both met, taking into account the availability of alternative materials: (a) the residual risk estimate indicates that the TSE risk has been controlled at an acceptable level; (b) the medical benefit arising from the intended use of the device is judged to outweigh the residual risk estimate. Guidance on risk management applicable to TSE agents is given in Annex D. Acceptability can be based on conformity with requirements specific to some animal materials given in Annex C or requirements relevant to sourcing, collection and handling of bovine materials given in ISO 22442-2:2015, Annex A. Regarding the TSE residual risk, specific considerations are provided in Annex C. Some derivatives such as tallow derivatives, animal charcoal, milk derivatives, wool derivatives and amino acids manufactured according to conditions mentioned in Annex C are considered as presenting an acceptable TSE risk. Where the TSE risk has not been controlled at a level that presents an acceptable level of risk to users or recipients, the overall risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations.

Evaluation of Overall Residual Risk Acceptability

The evaluation of the overall residual risk acceptability shall take into account the balance between the residual risk after implementation of all risk control measures and the expected medical benefit, as compared to available alternatives. Where residual risks exist with regard to the contamination with transmissible agents, the evaluation should specifically discuss the risks and benefits of—using alternative materials that do not present the risk of contamination with these transmissible agents, such as synthetic materials, materials from other animal species or materials from human origin, and—applying whole product alternatives for the same intended purposes. Where the risk has not been controlled at a level that presents an acceptable level of risk to users or recipients, the overall risk may only be judged acceptable when balanced by exceptional benefit and feasibility considerations.

Documentation

The rationale that the risk is acceptable shall be documented in the risk management file.

Production and Post-production Information System

Manufacturers shall ensure that the system will identify changes in the zoonosis status of the chosen source of animal materials.

2 Part 2: Controls on Sourcing, Collection and Handling

2.1 Scope

This part of ISO 22442 specifies requirements for controls on the sourcing, collection and handling (which includes storage and transport) of animals and tissues for the manufacture of medical devices utilizing materials of animal origin other than in vitro diagnostic medical devices. It applies where required by the risk management process as described in ISO 22442-1. Selective sourcing is considered to be especially important for transmissible spongiform encephalopathy (TSE) risk management. The manufacturers should refer to ISO 22442-3 for information on the validation of the elimination and/or inactivation of viruses and TSE agents. This part of ISO 22442 does not cover the utilization of human tissues in medical devices.

2.2 Terms and Definitions

- **Collection:** removal of tissues from animals
- **Low-risk herd:** herd of bovine animals in which, for at least the previous 8 years:
  (a) There has been documented veterinary monitoring
  (b) There has been no case of BSE
  (c) There has been no feeding of mammalian-derived protein
  (d) There is a fully documented breeding history
  (e) There is a fully documented use of veterinary medicines and vaccines
  (f) Each animal is traceable
  (g) Genetic material has been introduced only from herds with the same BSE-free status
- **Veterinarian:** person designated by the relevant competent authority as suitably qualified for the responsibility delegated to him or her relating to ante- and post-mortem inspection of animals and/or relevant certification

2.3 Quality System Elements

A documented system shall be established and maintained to control the quality of materials of animal origin and shall be verified by the medical device manufacturer. This system shall address the animal source and the following factors:

(a) Specification of the geographical origin (such as country or region) of the animal material, state of health of the animals and acceptance criteria for animals taking into account the source species, perceived risk from pathogens and abil-

ity to obtain appropriate assurances. The geographical origin can include the animal's place of birth and the countries or regions in which it has lived during its lifetime as well as its place of slaughter. It is advisable that the manufacturer document the extent to which the geographical origin of the animal can be traced taking into account the application of risk management.

(b) Hygiene and quality assurance requirements to be met by the slaughterer including the provisions in the slaughterhouse to prevent cross-contamination within and between animals.

(c) Procedures for the collection, preservation, handling, storage and transport of materials of animal origin.

For the control of processed animal material suppliers, the medical device manufacturer shall document, to the extent feasible, the practices of the specialized industries to which clauses of the various parts of ISO 22442 have been applied. Manufacturers should apply relevant provisions of ISO 22442 to natural substances such as milk, hair and wool, although these are not covered by the definition of derivatives.

Procedures

The documented procedures and instructions required by this part of ISO 22422 shall be established, implemented and maintained. These procedures and instructions shall be approved on issue and shall be controlled as follows. The manufacturer shall establish and maintain procedures to control all documents and data that relate to the requirements of this part of ISO 22442. These documents shall be reviewed and approved for adequacy by authorized personnel prior to issue. This control shall ensure that (a) the pertinent issues of appropriate documents are available at all locations where operations essential to the effective functioning of the quality system are performed and (b) obsolete documents are promptly removed from all points of issue or use. Changes to documents shall be reviewed and approved by the same functions/organizations that performed the original review and approval unless specifically designated otherwise.

Personnel

Responsibility for the collection, handling and storage of materials shall be assigned to qualified personnel as follows. The manufacturer shall establish and maintain procedures for identifying the training needs and provide for the training of all personnel performing activities affecting quality. The manufacturer shall ensure that personnel performing specific assigned tasks are qualified on the basis of appropriate education, training and/or experience as required. Appropriate records of training shall be maintained.

Current Regulatory Requirements and Guidance

Due account shall be taken of relevant current regional regulatory requirements or guidance including the OIE International Animal Health Code.

2.4 Sourcing

The animal material shall not be compromised by cross-contamination before, during or after slaughter. Animals shall be confirmed as having been declared fit for human consumption. It is the responsibility of the manufacturer to ensure that the material is fit for its intended use.

Species and Strain

For each material or derivative, the risk of certain diseases is dependent on the animal species and possibly strain, and this shall be taken into account for the establishment of control measures.

Geography

The risk of certain diseases is dependent on the geographical origin and this shall be taken into account for the establishment of control measures. Geographical origin can include conception, birth, rearing and slaughtering. If required by the risk management process, in the case of domesticated/farmed species, the geographical region/country of birth and the summary of main locations of residence up to time of slaughter shall be recorded. In the case of wild species, the region/location of capture and the country/region of birth shall be recorded if known. The use of wild mammalian species shall be addressed in the risk assessment.

2.5 Inspection

Sourcing of animal material shall be subject to control and individual inspection by a veterinarian. There will, however, be some source species where this is not possible (e.g. fish, crustaceans). If individual animals cannot be inspected, the justification for this shall be documented and a relevant sampling plan provided. Bovine, caprine, cervid, equine, ovine and porcine species shall be subject to ante-mortem veterinary inspection. Animals showing locomotive system abnormalities or neurological disorders shall not be used for the production of medical devices except for tallow derivatives, animal charcoal and amino acids that are acceptable. The

inspection shall include at least the following: (a) visual inspection; (b) palpation of specified organs; (c) incision of organs and lymph nodes; (d) investigation of anomalies, e.g. inconsistency, colour and smell; and, (e) if necessary, laboratory tests. Where indicated by risk assessment, for materials (including pooled blood supplies) for direct use in medical devices and that are not subject to a validated process to reduce TSE risk in line with ISO 22442-3, consideration shall be given to the application of a test for the presence of TSE in the source animal. Animal tissues derived from certain species (e.g. fish, crustaceans) require a modified approach since veterinary surveillance is not practicable in the same way as for other animal tissues. Manufacturers should apply relevant sections of this part of ISO 22442 to such materials but may need to rely on other procedures which have been shown to be effective for risk reduction.

Certification

Material of animal origin intended for utilization in medical devices shall originate from animals confirmed by a veterinarian as being fit for human consumption. Records to demonstrate conformance with veterinary inspection criteria at the abattoir, certificate details and source shall be available. For species where such certification by a veterinarian cannot be obtained, a status equivalent to "fit for human consumption" is required such as a confirmation of apparent good health.

2.6 Traceability

Where the risk management undertaken according to ISO 22442-1 indicates that it is both necessary and feasible, a traceability system shall be established. The extent of traceability shall be defined by the outcome of the risk assessment taking into account those official information systems that exist.

2.7 Collection

Materials derived from TSE susceptible species (including pooled blood supplies) intended for direct use in medical devices and that are not subject to a validated process in line with ISO 22442-3 to reduce TSE risks to an acceptable level determined by the risk management process shall be harvested from slaughterhouses designated by the medical device manufacturer. The manufacturer shall be responsible for ensuring that the collection of the material is conducted in accordance with the documented procedures. The manufacturer shall review and specify the systems for certification and traceability when tissues of animal origin are pooled at the place of slaughter or subsequently. The limits of pooling permitted shall be justified and documented.

2.8 Handling

If any material of animal origin requires further dissection or trimming, it shall be removed as soon as possible to an area separate from that used for slaughtering and collection. This area shall be suitably equipped and maintained at an appropriate level of cleanliness and environmental protection. Implements for dissection and trimming shall be kept clean to minimize risk of cross-contamination. Ideally, a dedicated set of tools should be used for trimming and kept separate from the ones used for harvesting. Source materials to be utilized in medical devices shall be segregated for delivery according to a documented procedure. The manufacturer shall be responsible for ensuring that the handling of the material is conducted in accordance with the documented procedures.

2.9 Storage and Transport

Collected material shall be stored and transported in closed containers. The conditions for storage and transport shall not compromise compliance with the relevant qualities of the animal material, in particular, by environmental or enzymatic degradation or microbial proliferation. The manufacturer shall be responsible for ensuring that the storage and transport of the material is conducted in accordance with the documented procedures.

3 Part 3: Validation of the Elimination and/or Inactivation of Viruses and Transmissible Spongiform Encephalopathy (TSE) Agents

3.1 Scope

This part of ISO 22442 specifies requirements for the validation of the elimination and/or inactivation of viruses and TSE agents during the manufacture of medical devices (excluding in vitro diagnostic medical devices) utilizing animal tissue or products derived from animal tissue, which are non-viable or have been rendered non-viable. It applies where required by the risk management process as described in ISO 22442-1. It does not cover other transmissible and non-transmissible agents.

3.2 Terms and Definitions

– **Model TSE agent:** TSE agent that displays a known resistance to physical and/or chemical processing used as reference by analogy for the inactivation of relevant TSE agents and thereby demonstrating the effectiveness of the process used for inactivation

- **Model virus:** virus that displays a known resistance to physical and/or chemical processing used as reference by analogy for the inactivation of relevant viruses and thereby demonstrating the effectiveness of the process used for inactivation
- **Overall reduction factor:** sum of the reduction factors of the individual process steps
- **Permissive cell:** cell that can become infected with the virus under study and in which that virus replicates
- **Reduction factor**: ratio of the virus or TSE agent load in the relevant material used or the device prior to the inactivation or elimination step and the virus or TSE agent load after the inactivation or elimination step when it is ready for the next step in the manufacturing process, expressed as the number of tenfold reduction
- **Relevant TSE agent:** TSE agent known to, or likely to, contaminate the source material or other materials used in the manufacturing process
- **Relevant virus:** virus known to, or likely to, contaminate the source material or other materials used in the manufacturing process
- R**evalidation:** set of documented procedures to confirm an established validation
- **Scaled-down process:** scaling down process at a specified reduced scale which simulates the performance parameters as used in the full-scale production process
- **Sterilization:** validated process used to render a product free of all forms of viable microorganisms
- **Validation documented:** procedure for obtaining, recording and interpreting the results required to establish that a process will consistently yield product complying with predetermined specifications

3.3 Risk Management

Sourcing and Manufacturing Process

A documented system shall be established and maintained to control the source of raw materials of animal origin. ISO 22442-2 shall be used to meet this requirement as far as applicable. The manufacturing process shall be established to minimize the load of viruses and TSE agents in starting materials, intermediate products and finished products. Appropriate documented protocols and procedures shall be established to ensure that the validated processing parameters will be applied during the routine manufacturing processes.

Documented Procedures

The documented procedures and requirements of this part of ISO 22442 shall be implemented. Documentation and records shall be reviewed and approved by designated personnel. Procedures for any literature review and/or any inactivation study

shall be documented, and records shall be retained for a period defined by the manufacturer.

Calibration

An effective system shall be established, documented and maintained for the calibration of all controlling, indicating and recording instruments used for validation.

Equipment

Appropriate equipment as specified in a protocol shall be used. All equipment requiring planned maintenance shall be maintained in accordance with documented procedures. Records of maintenance shall be retained. In particular, any equipment shall be capable of delivering its intended process within defined limits. In addition, if the equipment used during validation is not identical to that used in normal production cycles, adequate documentation shall be available to demonstrate that the performance parameters are equivalent to those used in the production cycle.

Experimental Systems

Additional parts of the experimental systems used for validation studies such as chemicals, cell systems and laboratory animals shall be adequately identified, justified, controlled and documented.

3.4 Literature Review

Conduct of the Literature Review

A literature review shall be performed in order to identify and analyse data on the elimination and/or inactivation of viruses and TSE agents. Technical information from the literature review shall be used in optimizing the design of an inactivation and/or elimination study. Any extrapolation based on the inactivation of viruses and TSE agents shall be justified and documented. Intrinsic variability of materials of animal origin utilized in medical devices and of manufacturing processes can lead to misinterpretation of the validity of published data and shall be taken into account.

Viruses

The manufacturer shall demonstrate whether the literature review provides an indication of which inactivation and/or elimination steps are likely to be effective. A literature review is a prerequisite to performing a viral inactivation study. In exceptional cases, if a manufacturer chooses not to perform a study, this shall be justified and documented. If the available information does not support the elimination and/or inactivation of viruses, then an alternative risk management strategy shall be implemented (see ISO 22442-1).

TSE Agents

The literature review shall consider which of the published methods for elimination and/or inactivation of TSE agents are likely to be suitable for the medical device under consideration. In particular, the materials of animal origin and manufacturing processes referred to in the literature shall be comparable to those used for the medical device under consideration. A validated inactivation study shall be performed when the comparability of materials and processes cannot be demonstrated or specific claims are made for inactivation of TSE agents by the manufacturer. If the available information does not support the elimination and/or inactivation of TSE agents, then an alternative risk management strategy shall be implemented.

3.5 Elimination and/or Inactivation Study of Viruses and TSE Agents

Protocol

The protocol for a study to demonstrate the elimination and/or inactivation of viruses and TSE agents during manufacture shall detail the following including, if applicable, values and acceptability criteria:

(a) The identified risks associated with the tissue concerned (ISO 22442-1).
(b) Identification of the relevant agent(s).
(c) The rationale for the choice of the particular combinations of model agents: The models for an elimination and/or inactivation study shall be chosen by the manufacturer; the justification for the choice of model(s) shall be documented.
(d) Identification and definition of the manufacturing stage(s) chosen to eliminate and/or inactivate the relevant viruses and TSE agents.
(e) Documentation of any scaling down, including demonstration of the validity of the scaled-down version of the manufacturing process.
(f) The methods of calculation for the reduction factors.

Conduct of the Study

The study shall be conducted in accordance with the protocol.

3.6 Final Report

A final report shall be compiled containing:

- The literature review
- A critical evaluation of the data obtained during any elimination
- Inactivation study undertaken
- An overall conclusion
- Reference to this part of ISO 22442

3.7 Review of Final Report

Procedures for a review of the final report by persons designated as responsible shall be documented. A review of the final report shall be conducted when significant changes in the manufacturing process(es) occur and/or when relevant information not previously considered in the final report becomes available, e.g. valid scientific evidence, scientific literature and authoritative publications. If necessary, corrective actions and/or additional studies shall be undertaken and reported to revalidate the manufacturing process. Records of any review of the final report shall be retained. The manufacturer shall assure that all critical parameters identified in the final report are monitored and controlled during manufacture.

4 Part 4: Principles for Elimination and/or Inactivation of Transmissible Spongiform Encephalopathy (TSE) Agents and Validation Assays for Those Processes

4.1 Scope

This technical report offers suggestions for designing and conducting validation assays to help determine if processes used in the manufacture of medical devices derived from non-viable animal tissues might serve to reduce the risk of iatrogenic transmission of transmissible spongiform encephalopathies (TSEs). The TSE-removal methods used to process animal tissues should also reduce the risk of transmitting TSE infections via non-viable tissues of human origin; this technical report

does not address this issue. Some current information on human tissues and TSEs is presented which may be applied by analogy to other animal tissues.

4.2 Terms and Definitions

For the purposes of this document, the terms and definitions given in ISO 22442-1, ISO 22442-2, ISO 22442-3 and ISO 14160 apply.

4.3 Elimination of TSE Agents: Basic Considerations

TSEs of Concern

BSE of cattle is the only TSE of animal origin known so far to have transmitted disease to humans (i.e. a zoonosis). Scrapie, while of theoretical concern, has not been recognized as a zoonosis in spite of hundreds of years of experience. Nonetheless, some competent regulatory authorities have adopted precautionary policies that discourage the sourcing of ovine-derived and caprine-derived injectable materials from herds with a history of scrapie. The susceptibility of sheep and goats to infection with the BSE agent has posed another more recent concern. Although pigs have been experimentally infected with the BSE agent, they were not infected when exposed by the oral route, and no naturally transmitted porcine TSE has been recognized, and most authorities remain generally satisfied that porcine tissues are an unlikely source of human exposure to any TSE agent. The same thing is true for tissues of other animals less commonly used in the manufacture of medical devices, such as horses.

Animal Tissues of Concern

Examples of animal tissues currently used in their non-viable form to manufacture medical devices include porcine heart valves, bovine pericardium and bovine collagen. While none of these tissues have been demonstrated to contain a TSE agent, experiments with animal tissues have been very limited in number, and the assays used vary in sensitivity of detection. Furthermore, it is conceivable that almost any animal tissue collected as part of routine slaughter might be accidentally contaminated with higher-risk tissues. Regulations and procedures requiring removal, segregation and safe disposal of “specified-risk” materials from animal carcasses—especially from carcasses of older animals—should reduce but not completely eliminate this risk. The European Commission has recently proposed “risk proportionate rules for animal by-products” to clarify and facilitate risk management in selection of source materials of animal origin.

Tissues Infected with TSE Agents

Agents might contaminate tissues in two ways: (1) a tissue infected during the TSE disease process and (2) infectivity introduced into the tissue from infected tissue (e.g. due to contact with tissues of the nervous system or lymphoreticular cells or from blood in the tissues). This second or "exogenous" source of contamination with a TSE agent might occur during harvesting of the tissue from an infected source or from instruments or surfaces contaminated with TSE agent from a previously handled source. These distinctions are important for several reasons: Endogenously infected tissues (except for tissues of the CNS, which have been found to contain the great majority of total infectivity in the body of an infected animal) generally contain very small amounts of agent, so suitable models to validate methods for eliminating endogenous infectivity are logistically difficult to develop. Exogenous contamination is more easily modelled by intentionally spiking tissues with TSE agents of known provenance, biological characteristics and content of infectivity as defined by titrations in susceptible animals. The selection of model agents for validation studies is constrained by several considerations:

(a) Although the actual unpassaged TSE agent likely to be present in the tissue of concern might be considered most "relevant" for purposes of validating inactivation/removal studies, the infectivity titres in such agents are usually both unknown and lower than those of rodent-adapted agents.
(b) In handling of the BSE agent and rodent-adapted strains derived from BSE agent, regulatory authorities may require high-containment research facilities not widely available. In general, studies with rodent-adapted scrapie agent have been considered acceptable, keeping in mind that reported resistance of various strains of TSE to inactivation procedures has not been uniform.

4.4 Potential Methods to Eliminate TSE Agents

Methods for Inactivating Infectivity Most authorities recommend that, whenever possible, TSE agents potentially contaminating source materials be inactivated rather than simply separated from the raw materials. The presence of residual active agent might pose a continuing danger of later accidental contamination of a tissue-derived product as well as contaminating manufacturing facilities and non-disposable equipment. However, unfortunately, most of the physical and chemical methods known to be effective for inactivating TSE agents are relatively harsh and often impair the functional properties of tissues. For sanitizing the facilities and processing equipment that cannot be destroyed after single use or protected from direct contact with potentially contaminated materials, decontamination methods that reliably inactivate TSE agents are preferred to those that simply remove the agents.

Physical Methods for Inactivating TSE Infectivity

Heat When suspensions of tissue from scrapie-infected rodents were rapidly heated with continuous stirring, relatively rapid loss of infectivity occurred within a few minutes reaching the assay limit of detection. However, macerates and dried preparations of TSE agents retained some infectivity even after long exposures to heat. Dry heat appears to be less effective than moist heat for inactivating TSE agents. One series of studies even found small amounts of infectivity in ash from scrapie agent incinerated in an oven at temperatures up to 600 °C, though not at a higher temperature. Tissue devices are unlikely to tolerate heat treatments adequate to inactivate TSE agents without loss of function. There have been suggestions that for adequate decontamination of TSE agents, one should specify exposure to steam in a porous-load autoclave for at least 18 min at 20-bar pressure. This has been shown to be ineffective. The World Health Organization Consultation warned that such treatment was unlikely to decontaminate a surface soiled with dried-on tissue from a TSE-contaminated source. A consultant to the US CDC cautioned that many pathogens survive heat and chemical treatments when contaminated surfaces have not been thoroughly cleaned and that thorough cleaning of critical surfaces must be employed for safe reuse of all medical devices.

Radiation The TSE agents have resisted inactivation by both ultraviolet and ionizing radiations.

Chemical Methods for Inactivating TSE Infectivity

Alkaline Hydrolysis Treatments Exposure to sodium hydroxide (≥1N, especially at elevated temperatures) has been found effective in removing infectivity from both aqueous suspensions and tissues dried onto surfaces and is widely used in laboratories dealing with TSE agents. The hazards posed by NaOH are well known. The corrosive properties of NaOH for autoclaves seem to have been exaggerated, so long as solutions are carefully contained to prevent direct contact with critical surfaces of the chamber. Calcium hydroxide treatments, widely used in the manufacture of gelatines, appeared to be much less effective than NaOH in removing scrapie and BSE infectivity from spiked preparations of animal bones, although the addition of heat was highly effective. A number of alkaline-based formulations (mixtures of chemicals with alkaline sources) are claimed to be as effective as low concentrations of alkalinity. These effects appear to be formulation-specific and will depend on the formulation, temperature and concentration of the specific product. These treatments are less destructive to tissues, but the studies to date have not compared their efficacy to higher concentrations of alkali treatments.

Acid Treatments TSE agents have been substantially if not completely inactivated by exposures to concentrated formic acid and, more recently, to acetic acid in a solution of sodium dodecyl sulphate. Sodium hypochlorite (household chlorine bleach

at concentrations ≥5%) has been found effective in removing TSE infectivity from scrapie-contaminated suspensions and surfaces and is widely used in situations where the corrosive effects on metals are not a problem. Chloramine and other halides have been found less effective. Liquid hydrogen peroxide has also been found to lack utility for decontaminating TSE agents, although in low-temperature gaseous form it might be more effective.

Treatments with Phenolic Disinfectants

A proprietary phenolic disinfectant has been reported to eliminate scrapie infectivity from contaminated suspension to the limit of detection. Treatment with phenol itself failed to eliminate infectivity.

Protease Treatments

Stimulated by the widely accepted prion theory, studies investigating effects on infectivity of TSE agents from several protease treatments have been investigated, yielding variable results. As noted above, thorough cleaning is undoubtedly important in freeing surfaces of infectivity, and protease treatments probably facilitate that process. Whether proteases have an additional specific effect of inactivating TSE agents by cleaving the prion protein is less clear.

Guanidine and Other Chaotropic Chemical Treatments

Treatments with guanidine and other chaotropic chemicals have been found to reduce infectivity. Some reports suggested that the apparent inactivation was reversible when the chaotropic chemical was removed.

Combined Treatments

Limited experience suggests that combinations of TSE-inactivating treatments having different chemical and physical actions might be more effective than either treatment used separately. Examples of potentially effective combined treatments have included NaOH with heat, including boiling in neutral detergent and acetic acid in detergent solution. Potential damage to autoclaves may be mitigated by the use of covered containers to isolate the NaOH from the autoclave interior.

Ineffective Treatments

Ethylene oxide gas, alcohols, mercurial disinfectants and a number of other treatments commonly used to sanitize or sterilize surfaces have not been found useful for decontamination of TSE agents; research with such treatments has been limited. Aldehydes not only failed to inactivate TSE agents; they may have stabilized the infectivity. More ineffective treatments may be found in the document from the UK government, which lists ineffective treatments.

4.5 Methods for Removing TSE Infectivity Without Inactivating Infectivity

Although physical methods such as chromatography, sedimentation, filtration and partition of fractions offer some promise for reducing amounts of TSE infectivity in complex biological mixtures (e.g. blood and its components and plasma and its fractions), it is unlikely that selective removal of infectivity from intact non-viable tissues would be feasible.

4.6 Experimental Validation of Methods for Eliminating TSE Agents from Medical Devices Utilizing Non-viable Animal Tissues

Although limited study has been attempted using methods expected to reduce if not eliminate TSE agents exogenously contaminating human non-viable tissues, few if any studies have directly attempted to decontaminate animal-derived tissues. As outlined in ISO 22442, all parts, the more appropriate method for reducing risk is careful selection of low-risk source animals and tissues and good manufacturing processes (GMPs) to reduce opportunities for exogenous contamination with neural tissues and, to a lesser extent, lymphoreticular and intestinal tissues.

Defining of Product Families for Purposes of Designing TSE Process Validation Studies

For purposes of this document, the definitions of product families described in AAMI TIR37:2007 Section 4 that are appropriate to evaluation of validation assays for elimination/removal of TSE agents from medical devices utilizing non-viable animal tissues should apply here as well. The products selected for experimental validation should, as closely as feasible, resemble the manufactured product of concern and be considered by one or more expert consultants to constitute an acceptable realistic representative of a product family.

Selection and Testing of Product for Establishing and Verifying the Infecting Dose of TSE Agent

For purposes of this document, the considerations for nature of the test product sampling conditions, sample item portions, considerations regarding use of multiple batches and assays of fluids extracted from test products that are appropriate to evaluation of validation assays for elimination/removal of TSE agents from medical devices utilizing non-viable animal tissues should apply here as well. Note that assays of TSE agents, whether by preliminary immunoassays of protease-resistant PrPTSE or—especially—by subsequent bioassay in animals, are considerably more technically difficult, time-consuming (months or years for bioassays) and expensive than are cultures of bacteria and fungi, and that must be taken into account when selecting numbers of replicates for testing.

TSE Agent Spiking Materials

Limited but accumulating evidence suggests that, while all TSE agents share most biological and physical properties, including unusual resistance to inactivation by a variety of treatments, strains have differed substantially in that resistance. It seems prudent to select for spiking a tissue infected with a strain of TSE agent more rather than less resistant to the inactivation procedure under study so long as the spike material is relevant to the manufacturing process. While it might be argued that worst-case scenarios are unrealistic representations of manufacturing situations, the logistics of validation models have usually required that tissues containing very high concentrations of TSE agent (usually meaning infected brain tissue suspensions, fragments or macerates) be employed as spiking materials. It must be acknowledged that such materials, most often prepared from brains of rodents infected with rodent-adapted strains of TSE agent (especially scrapie agent), might not closely resemble naturally infected tissues either in amounts or biological and physical properties of the agent or in some properties of the matrix (tissue of origin). However, in general, it has not been feasible to validate processes for eliminating TSE agents from raw materials except by spiking with rodent-adapted TSE agent strains in rodent brain tissues for several reasons.

(a) Titres of TSE agent in naturally infected tissues are generally not known, nor is the susceptibility of available rodents to infection with field isolates (often poor). Tissues other than brain have much lower titres of both PrPTSE (often not detectable) and infectivity than brain.
(b) Well-characterized standard reference materials prepared from tissues of naturally infected animals are not yet widely available.
(c) Transgenic mice or other rodents—e.g. European bank voles consistently susceptible to infection with field isolates of TSE agents—are not generally available except in a few research laboratories.

4.7 Availability of Bioassay Animals

Rodent-adapted TSE agents, commonly derived from strains of sheep scrapie but recently from BSE as well, have been used in pilot studies to investigate methods for eliminating infectivity experimentally spiked into various raw materials or intermediates. The 263K hamster-adapted strain of scrapie agent and similar strains assayed in golden Syrian hamsters have been especially useful. The 301V mouse-adapted strain of BSE agent assayed in conventional mice might be more predictive of the probable behaviour of BSE agent in bovine tissues.

Transgenic mice engineered to express amino acid sequences of other species in the PRNP gene may be useful in certain situations but pose several problems.

(a) Mice overexpressing prion proteins have developed non-transmissible neurological diseases histopathologically resembling TSEs later in life, which sometimes confused the interpretation of infectivity assays.
(b) Most lines of PRNP–transgenic mice can currently be obtained only as gifts from the developers.

Compared with some strains of conventional mice, the superiority of mice expressing bovine PRNP amino acid sequences has not been rigorously demonstrated to date, although some lines may prove to be more sensitive. (Human-derived TSE agents infrequently transmit disease to conventional mice, and—since assays using nonhuman primates have become increasingly unfeasible—transgenic mice expressing human PRNP amino acid sequences appear to offer the most practical assays of infectivity.) As noted above, European bank voles have been described as highly susceptible to a number of TSE agents; however they appeared to be relatively less sensitive than mice to the BSE agent and to the emerging Nor98 strain of scrapie agent, and, in any case, colony-raised voles are not widely available.

It might be argued that methods for eliminating the infectivity of animal-derived TSE agents should most appropriately be studied using materials from naturally infected animals assayed in susceptible animals of the same species; although that has been done to a limited extent to investigate pathogenesis of BSE by assays in calves and scrapie in sheep, it is generally not practical to study elimination of TSE infectivity in large animals.

Potential Development of Cell Culture Assays for Infectivity

Several cell lines have been described that support the propagation of selected TSE agents. Although the cells showed no recognizable cytopathic effect, PrPTSE could be detected. Such a cell culture assay has been reported to be much more sensitive than direct detection of PrPTSE in the original infected tissue. Unfortunately, cell culture assays have not been developed for detection of BSE agents, field isolates of scrapie agents from sheep or human-derived TSE agents. In addition, false-positive PrPTSE results have posed a problem. The development of reliable and sensitive

cell culture-based assays for animal TSE agents would greatly facilitate the validation of methods to eliminate the agents from animal-derived materials.

Correlations Between PrPTSE and Infectivity Assays

Although PrPTSE has usually been detected in tissues and tissue extracts containing TSE infectivity, a number of reports failed to demonstrate PrPTSE in materials containing considerable amounts of infectivity. Furthermore, immune reactive proteins with properties of PrPTSE have been found in tissues that did not contain detectable agent transmitting spongiform encephalopathy. Several investigators have asserted that it is possible to generate TSE infectivity from tissues of animals that were never exposed to the agents. This confusing situation urgently requires clarification but serves as a caution when interpreting results of assays for PrPTSE. Although several reports claimed that innovative assays for PrPTSE were more sensitive than rodent bioassays of infectivity, those claims remain to be independently verified in comparative blinded and randomized studies.

Reductions in Infectivity Compared with Failure to Detect at Limits of Detection

Confirmed reductions in amounts of infectivity estimated by assays can be considered informative so long as the tests have used robust methods with a sufficient number of replicate experiments and assays within each experiment to assure that results are repeatable. Just as for estimates of reductions in infectivity for other infectious agents, considerable caution must be exercised when relying on results of variable assays, and especially when reductions are less than 1000-fold. For that reason, some authorities have recommended that two validated infectivity-reducing processes, each based on a different chemical-physical principle, be employed in any manufacturing scheme claiming to reduce the risk of contamination. For biological products, FDA policies have recommended that each of the two processes reduce spiked infectivity by at least ten-thousand-fold before asserting a claiming that a manufacturing method is likely to reduce the risk of contamination with a defined pathogen to an acceptable level.

4.8 Requirements for Stepwise Reductions in PrPTSE and Infectivity Versus Whole-Process Validation

Although it would be especially reassuring to validate the effectiveness of an entire manufacturing process by eliminating substantial amounts of relevant TSE infectivity spiked into real starting material in a realistic pilot model, yielding a functional

end product completely free of detectable infectivity, such validation may not be achievable for several reasons. The input infectivity in starting material may be modest; various steps may greatly dilute the amount of original materials reaching the final product. This dilution introduces a sampling problem in the design of the experiment. If there is no infectious dose in a sample due to dilution, one will see a false-negative in the assay used. The solution to this problem is to test more samples, which is often not feasible. Surface-volume relationships are not maintained in scaled-down pilot models. Therefore, as for viral validations of biologic products, it is more often necessary to spike individual intermediate steps with model TSE agents, attempting to simulate realistic process conditions and conditioning of the intermediates, and then to infer probable overall effectiveness of a whole production scheme by adding orthogonal log reduction factors to yield a probable total log reduction value, keeping in mind attendant uncertainties.

Annexures

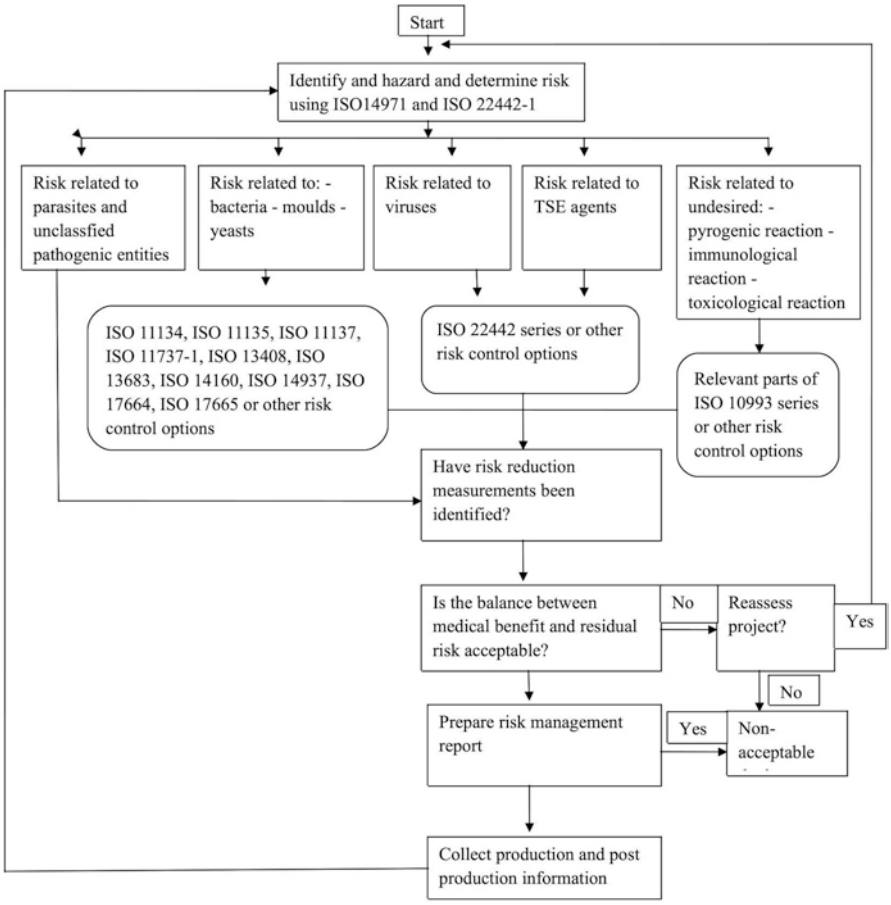
Annexure A: Guidance on the Application of This Part of ISO 22442

Application to Materials from Animal Sources This international standard is applicable to materials such as:

- Porcine heart valves, bovine bones, cattle ligaments and bovine pericardium
- Derivatives of animal tissues, such as chondroitin sulphate obtained from shark and collagen derived from hides, and of animal blood or serum
- Materials produced in vivo by relevant animals, e.g. antibodies utilized in the manufacturing process
- Starting materials such as bovine serum albumin, enzymes, culture media including those used to prepare working cell banks, master cell banks or master seeds for products such as hyaluronic acid

Application to Materials Supplied by Third Parties This part of ISO 22442 can be applied when the materials used by medical device manufacturers have been prepared from animal sources by third parties or subcontractors. An example is gelatine derived from animal hides or bones. In considering the risks associated with the use of these products, the medical device manufacturers should seek evidence from their suppliers as to whether relevant requirements of this international standard have been applied in assessing the suitability of the animal material or whether alternative approaches were applied.

Annexure B: Graphical Representation of Part of the Risk Management Process for Medical Devices Utilizing Animal Material



Annexure C: Special Requirements for Some Animal Materials Considering the Risk Management for TSE Agents

C.1 Collagen Collagen is a fibrous protein component of mammalian connective tissue. For collagen, documentation to demonstrate compliance with this part of ISO 22442 shall be provided, taking into account the relevant requirements of this

annex. When completing the risk management required by this part of ISO 22442, consider the following: For collagen produced from bone, the bone shall be sourced from countries with minimal exposure to BSE. Sourcing bone from countries with limited exposure to BSE shall be justified by reference to other applicable risk control measures. Bone shall not be sourced from countries where infection with the BSE agent is confirmed at a higher level, unless from a low-risk herd as defined in ISO 22442-2. For collagen produced from bones, the manufacturing conditions specified for gelatine are applicable.

– Collagen produced from hides and skins does not usually present a significant TSE risk provided that cross-contamination with potentially infected materials, for example, central nervous tissues, is avoided during their procurement. To demonstrate compliance with the requirements of this part of ISO 22442, it is necessary to incorporate measures to prevent cross-contamination and to document the measures that are adopted in the technical agreement between the collagen supplier and the medical device manufacturer to prevent such cross-contamination. Collagen shall be obtained from animals declared as fit for human consumption.

C.2 Gelatine Derived from Hides and Bones

Gelatine is a natural, soluble protein, gelling or non-gelling, obtained by the partial hydrolysis of collagen produced from bones, hides and skins, tendons and sinews of animals. For gelatine, documentation to demonstrate compliance with this part of ISO 22442 shall be provided, taking into account the relevant requirements listed in this annex. Gelatine shall be obtained from animals declared as fit for human consumption.

Hides as the Starting Material On the basis of current knowledge, hides used for gelatine production represent a safer source material when compared to bones. Gelatine produced from hides does not usually present a significant TSE risk provided that cross-contamination with potentially infected materials, for example, central nervous tissues, is avoided during their procurement. To demonstrate compliance with the requirements of this part of ISO 22442, it is necessary to incorporate measures to prevent cross-contamination and to document the measures that are adopted to prevent such cross-contamination in the technical agreement between the gelatine supplier and the medical device manufacturer.

Bones as the Starting Material Where bones are used to manufacture gelatine, the quality of the starting materials is the primary parameter that will ensure the safety of the final product. Therefore, the following shall be applied:

– Subject to national legislation, bone shall be sourced from countries with minimal or limited exposure to BSE. Bone shall not be sourced from countries where infection with the BSE agent is confirmed at a higher level, unless from a low-risk herd as defined in ISO 22442-2.
– Skulls and spinal cords shall be removed from the collected bones (raw/starting material) from cattle of a specific age as defined in national legislation.

– Additionally, vertebrae shall be removed from the raw/starting materials from cattle of all ages from countries with limited exposure to BSE.

C.3 Bovine Blood Derivatives General foetal bovine serum is commonly used in cell cultures. Foetal bovine serum should be obtained from foetuses harvested in abattoirs from healthy dams fit for human consumption, and the womb should be completely removed. The foetal blood shall be harvested in a dedicated space or area by cardiac puncture into a closed collection system using an aseptic technique. New born calf serum is obtained from calves aged less than 20 days and calf serum from animals aged less than 12 months. In the case of donor bovine serum, given that it can be derived from animals less than 36 months old, the BSE status of the donor herd shall be well defined and documented. In all cases, serum shall be collected according to specified protocols by personnel trained in these procedures and the precautions necessary to avoid cross-contamination with higher-risk tissues.

C.4 Stunning Methods If blood is obtained from slaughtered animals, the method of slaughter is of importance to ensure the safety of the material. It has been demonstrated that stunning by a captive bolt stunner with or without pithing, as well as by pneumatic stunner, especially if it injects air, can destroy the brain and disseminate brain material into the blood stream. There is evidence that non-penetrative stunning can cause some central nervous system (CNS) embolism. The stunning methods shall be described for the bovine blood collection process unless the material is sourced from a country of negligible geographical BSE risk. Where sourcing of blood is from countries with limited exposure to BSE, a non-penetrative stunner or electronarcosis shall be used for slaughter of animals over 12 months of age. The use of non-penetrative stunning shall be justified on the basis of an estimate of the risk of dissemination of brain particles into the blood.

C.5 Tallow Derivatives Tallow is fat obtained from tissues including subcutaneous, abdominal and intermuscular areas and bones. Tallow derivatives, such as glycerol and fatty acids, manufactured from tallow by rigorous processes, are thought unlikely to be infectious. For this reason, such materials manufactured under the conditions at least as rigorous as those given below shall be considered as presenting an acceptable TSE risk, irrespective of the geographical origin and the nature of the tissues from which tallow derivatives are derived.

C.6 Animal Charcoal Animal charcoal is prepared by carbonization of animal tissues, such as bones, using a temperature >800 °C. Irrespective of the geographical origin and the nature of the tissue, animal charcoal prepared under these conditions shall be considered as presenting an acceptable TSE risk.

C.7 Milk and Milk Derivatives Certain materials, including lactose, are extracted from whey, the spent liquid from cheese production following coagulation. Coagulation can involve the use of calf rennet, an extract from abomasums, or rennet derived from other ruminants. A risk assessment for lactose and other whey derivatives produced using calf rennet was performed and concluded that the TSE risk is negligible if the calf rennet is produced in accordance with the process

described in the CPMP risk assessment report. Subject to national legislation, milk derivatives manufactured according to the conditions below are considered as presenting an acceptable TSE risk: the milk is sourced from healthy animals under the same conditions as milk collected for human consumption; no other ruminant-derived materials, with the exception of calf rennet, are used in the preparation of such derivatives (e.g. pancreatic enzyme digests of casein).

C.8 Wool and Its Derivatives Wool and its derivatives, such as lanolin and wool alcohols, shall be considered in compliance with this part of ISO 22442, provided the wool is sourced from live healthy animals. Wool derivatives produced from wool that is sourced from slaughtered animals declared "fit for human consumption" are considered as presenting an acceptable TSE risk if the manufacturing process in relation to pH, temperature and duration of treatment meets at least one of the stipulated processing conditions listed as follows: treatment at pH ≥13 (initial; corresponding to concentrations of sodium hydroxide ≥0,1 mol/l) at ≥60 °C for at least 1 h; this normally occurs during the reflux stage of the organic-alkaline treatment; molecular distillation is at ≥220 °C under reduced pressure.

C.9 Amino Acids Amino acids can be obtained by hydrolysis of animal materials from various sources. Amino acids prepared using the following processing conditions are considered as presenting an acceptable TSE risk: amino acids produced from hides and skins by a process which involves exposure of the material to a pH of 1–2, followed by a pH >11 and heat treatment at 140 °C for 30 min at 3 bar; the resulting amino acids or peptides shall be filtered after production; analysis shall be performed using a validated and sensitive method to control any residual intact macromolecules with a justified limit set.

Annexure D: Information Relevant to the Management of TSE Risk

TSE The naturally occurring transmissible spongiform encephalopathies (TSEs) include scrapie (in sheep and goats), chronic wasting disease (in mule deer and elk), bovine spongiform encephalopathy (BSE) in cattle as well as kuru and Creutzfeldt-Jakob disease (CJD) in humans. It is difficult to detect agents causing these diseases in vivo. After latency periods of up to many years, the agents cause disease and, finally, lead to death. No means of therapy is known. Current information on the characteristics of the causative agents is limited. These agents are extremely resistant to most of the chemical and physical procedures that inactivate conventional viruses. They do not induce a detectable immune response. There are natural barriers which limit their interspecies spread of transmissible agent, but they can be crossed under appropriate circumstances. This is usually dependent upon strain, dose, route

of exposure and the species barrier. Studies in laboratory animals have shown that intracerebral inoculation is the most efficient route of transmission.

Risks for Humans There is considerable circumstantial evidence that the variant form of human CJD (vCJD) arose from BSE and it is prudent to accept that the BSE agent can be transmitted to man. This part of ISO 22442 therefore contains a number of requirements to ensure that risks are controlled if biological materials from species susceptible to TSE are used for the manufacture of medical devices. This annex provides guidance that should be followed to minimize the risks of contamination. It identifies where requirements elsewhere in this part of ISO 22442 are applicable and where information from other sources is relevant. All devices should be considered on a case-by-case basis.

Risk Management for TSE Agents The safety of a medical device, in terms of its potential for passing on a TSE agent, is dependent on a number of factors. The eight most important factors below should be analysed, evaluated and managed:

- Animal species used
- Geographical sourcing
- Nature of starting tissue
- Slaughtering and processing controls to prevent cross-contamination
- Methods used to inactivate or remove TSE agents
- Quantities of animal starting material required to produce one unit of the medical device
- Quantities of material of animal origin coming into contact with the patients and users
- Route of administration

References

1. BS EN ISO 22442-1:2015 Medical devices utilizing animal tissues and their derivatives Part 1: Application of risk management
2. BS EN ISO 22442-2:2015 Medical devices utilizing animal tissues and their derivatives Part 2: Controls on sourcing, collection and handling
3. BS EN ISO 22442-3:2007 Medical devices utilizing animal tissues and their derivatives Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents
4. ISO/TR 22442-4: Medical devices utilizing animal tissues and their derivatives — Part 4: Principles for elimination and/or inactivation of transmissible spongiform encephalopathy (TSE) agents and validation assays for those processes

ISO 11137: An Overview on Radiation for Sterilization of Medical Devices and Healthcare Products

Balu Venugopal, Sunitha Chandran, and Amita Ajit

1 Introduction

Sterilization, in the context of medical devices, aims to eliminate the pathogenicity associated with it by removing the number of microorganisms present on it. Any device before sterilization will have microorganisms even in low numbers, categorizing it to be nonsterile. In this context, sterility thus refers to the absence of viable microorganisms on medical devices. A ready to use medical device in humans for treatment, therapy or research has to be free of microorganisms, and the process employed for its sterilization has to follow the international standards to ensure validation of the sterilization process.

Apart from achieving sterility, methods to ensure sterility and its validation are also important. It is necessary that the method of sterilization implemented is reliable and reproducible with similar levels of performance every time. This stresses that the kinetics of inactivation of microorganisms employed should remain the same whenever the same sterilization methods are employed. In short, the achievement of its repeatability is of utmost necessity. The kinetics of inactivation by any sterilizing agent depends on the extent of treatment and the number of microorganisms surviving after treatment. So the process of sterilization employed should be able to provide appropriate microbicidal activity ensuring minimum probability for having a microorganism on the medical device post-sterilization. The standard

B. Venugopal
Department of Health Research, New Delhi, India

S. Chandran
SCTIMST-TIMed, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

A. Ajit (✉)
Scientific Consultant (Biologics) & Life Member, Kerala Academy of Sciences, Thiruvananthapuram, Kerala, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_8

specific probability values differ from country to country as per the regulatory requirements of the respective countries. However, to ensure uniformity of standards, international standards and guidelines are to be considered.

This chapter deals with the process of radiation sterilization of medical devices and its requirements in healthcare products as described by the International Organization for Standardization (ISO). Complying with ISO standards ensures consumer satisfaction by delivering quality products suiting the purpose and efficient use meeting international standards. This chapter thus describes the development, validation and routine control of the sterilization process including operational and performance qualification of the unit, routine calibration and maintenance. This chapter also discusses various methods employed to establish the sterilization dose for each specific product as per the ISO standards. The following document provides the guidelines for proper dose measurement, also termed as dosimetry to determine the amount of dose absorbed by each product to ensure complete sterilization

2 Sterilization by Irradiation

Sterilization by irradiation is one of the common methods of sterilization used in the medical industry and is considered safe and cost-effective. Irradiation is generally considered to be advantageous over other sterilization methods due to its better penetration resulting in complete sterilization and is independent of temperature and pressure fluctuations. The effect or impact of radiation depends on the resistance of microorganisms to radiation and the microorganism's capability to repair single-strand breaks due to the activity of their DNA repair enzymes. Means of radiation can either be a radionuclide ^{60}Co or ^{137}Cs (gamma irradiation), a beam from an electron generator or an X-ray generator.

2.1 Characterization of the Sterilizing Agent

Sterilization by radiation requires an irradiator that can generate a radiation beam. The microbicidal activity of the radiation process employed will be critical in determining the sterility of the product or the sterilization efficiency of the process employed. The effect of irradiation on the functional efficiency of the product post-sterilization should also be assessed to identify the appropriate sterilization method. For example, in the case of X-ray irradiator, the probability of induced radioactivity in the sterilized product has to be assessed. The quality and composition of the material used in the manufacture of the medical device may also influence the use of radiation in the sterilization process. Effect of the radiation dose on the surrounding environment is yet another parameter to be considered while selecting a sterilization method. All these parameters should be considered for identifying and

characterizing an appropriate sterilization method for safe and effective sterilization.

2.2 Characterization of the Equipment

The equipment/the irradiator used for the sterilization should ideally be designed in accordance to the ISO standards that will meet the requirements of the material to be sterilized, and the software used should be able to deliver the required process outcome. The general requirement for an irradiator will include the following as per ISO standard 11137-1:

- The operating requirements, specifications and routine maintenance schedule of the irradiator
- Type of radionucleotide or gamma irradiation system for a gamma irradiator
- The characteristics and energy of the beam for electron and X-ray beam irradiators
- Construction and operation of the conveyor system and its details
- Dimension and nature of irradiation containers
- Position and status display of the gamma source when it is operational
- The premises of the irradiator
- Procedure to segregate irradiated products from non-irradiated products
- Procedure to cease the irradiation and conveyor movement as and when required

2.3 Sterilization Process

Sterilization process includes a series of actions or operations needed to achieve the specified requirements for sterility. For a product to be sterilized effectively, the maximum microbicidal potential of the irradiation dose has to be ensured. This is calculated by determining the maximum acceptable dose and the sterilization dose. The maximum acceptable dose is the highest dose used to sterilize the product without compromising its specified functional requirements including safety, quality and performance throughout its life after sterilization. Before radiation sterilization, it is necessary to determine if the material including its packaging can withstand the effect of radiation employed. Various materials interact with the ionizing radiation differently, and it is important to identify the highest safe dose to be used for sterilizing each material component without affecting their shelf life.

The basic technical requirements for performing a sterilization process and its validation include:

- The supply of product/product representatives including its packaging material that has to be irradiated

- A facility to assess product function post-sterilization to confirm if any functional requirements are compromised
- An irradiator/appropriate source of radiation that can deliver the required amount of radiation dose
- Settings to determine and establish the sterilization dose
- An ISO competent microbiological laboratory for bioburden determination
- Requirements for performing the dosimetry

3 Validation

Validation involves generation and storage of documented procedure for obtaining, recording and interpreting the results that will establish if the process consistently yielded the product complying with predetermined specifications. This includes the installation of the irradiator, conducting routine control of sterilization process including the operational and performance qualification. All the sterilization records should be traceable at any point of time for any batch of medical devices. Proper auditing should be done to analyse records and servicing activities associated with the sterilization instrument and its process. Part of ISO 11137-1:2015, "Sterilization of health care products—Radiation: Requirements for development, validation and routine control of a sterilization process for medical devices", describes validation and routine control in detail.

Installation validation includes testing and documentation of the functioning of the irradiator, conveyor system and ancillary equipment including the software and the irradiation source at the time of installation. Any modification or alteration at the time of installation has to be recorded. This usually includes the initial calibration of the entire instrumentation set-up of the irradiator pertaining to its performance, monitoring and recording.

Validation for operational qualification determines the capability of the equipment to deliver the exact doses and range of doses as specified in the software as per the requirement of the products to be irradiated. Dose mapping also forms a part of operational qualifications where it determines the distribution of irradiation doses at various parts of the irradiation container. Dose mapping has to be performed in an irradiation container when it is filled to its full capacity using a product of homogeneous density that will allow precise dose mapping. In case of gamma and X-ray irradiators, the time setting of generation and duration of the dose has to also be validated in correspondence to the conveyor speed.

The performance qualification as defined by ISO is the "process of obtaining and documenting evidence that the equipment, as installed and operated in accordance with the operational procedures, consistently performs as per the predetermined criteria and thereby yields the product meeting its said specification". Validation for performance qualification will allow continuous monitoring and recording of the performance delivered by the irradiator as specified according to the sterilization requirements. Dose mapping is routinely performed to determine the location and

magnitude of minimum and maximum dose. Apart from validating the installation and performance of the irradiator, the process of irradiation also has to be validated.

The process specification in general includes the following:

- Product dimensions including density and orientation packaging details
- Pattern of product loading in the irradiation container
- The conveyor path(s)
- The maximum acceptable dose
- The sterilization dose
- Time taken from manufacturing to completion of irradiation
- The routine dosimeter monitoring position
- Dose at the monitoring position(s), minimum and maximum doses

Routine control and monitoring of the irradiator and the process of sterilization is important to maintain the quality control of the sterilization process. This includes validation of the product requirements for irradiation, validation of dosimetry and the system requirements. The irradiated products should be verified for complete sterilization using appropriate methods like sterilization indicators. There should be appropriate mechanisms to segregate sterilized and non-sterilized products which are validated. All the product validation procedures including periodic tests, calibrations, maintenance tasks and necessary requalification should be performed and recorded before the product is released from the sterilization department. The initial validation has to be followed by continuous monitoring for system and process effectiveness and sterilization dose audits. This will ensure the performance qualification of the system and the process in appropriate intervals leading to complete sterilization.

4 Establishing Sterilization Dose for Irradiation of Products

ISO 11137-2:2015, Sterilization of health care products—Radiation; Part 2: Establishing the sterilization dose, describes methods that can be used to determine the sterilization dose. Sterilization dose is the minimum dose required to achieve sterility. Determination of sterilization dose is influenced by various factors, and depending on the parameters assessed, there are various methods to determine the sterilization dose.

4.1 Factors Influencing the Bioburden on a Product

The sterilization process and dosage will be determined by the bioburden levels on the product to be irradiated. Bioburden is defined as the population of viable microorganisms on or in product and/or sterile barrier system. Bioburden levels are classified as low, moderate and high depending on the initial amount of microorganism

present on the product before irradiation. A bioburden level of 1–10 is considered as low, 10–100 is considered moderate, and 100–1000 is considered high. The product to be sterilized also plays an important role in determining the bioburden and sterilization dose settings. The material with which the product is manufactured, product size and design, the manufacturing process and environment are factors that influence the intensity of bioburden on an item. Along with the above-mentioned parameters, the number and type of microorganisms on the product also determine the amount of bioburden on the product and thereby the dose requirement for sterilization.

4.2 Identifying a Product Family

It is not necessary to validate and demonstrate the sterility of every product that undergoes irradiation for sterilization. Depending on the number of products per batch and the number of batches to be sterilized, either a few batches or a few numbers of products from each batch can be validated for demonstrating successful sterilization. The product used for validation of sterilization would thus represent a product family. Forming product families will save time and cost for establishing and validating the sterilization dose for similar products. For a product to be used as a representative of the product family, it has to have a similar bioburden intensity (number and type of microorganism on the product) as that of the product family. Other parameters include the size, complexity of the product and its environment of manufacturing.

The products used for the determination of sterilization dose and validation can be either a master product, equivalent product or simulated product. A master product refers to a product which presents a higher bioburden possibility than any other material in the product family. A group of products can be considered equivalent when the group members require the same sterilization dose for irradiation purpose. The other parameters to be considered include the manufacturing volume and availability of the product. To reduce the wastage of products for dose determination, simulated or surrogate products can also be used for establishing sterilization dose and validation. A simulated product should be solely made for the establishment and validation of sterilization dose and is not meant for clinical use. For a surrogate product to replace the original product, it has to represent an equal or higher bioburden than the original product. The simulated product should also be similar in terms of raw material used for manufacturing, size of the product and manufacturing process.

4.3 Sample Item Portion

A defined portion of a healthcare product that is to be tested and used for establishment and validation of sterilization dose is called a sample item portion (SIP). The value of SIP is calculated based on the nature of the product to be sterilized and

based on either its length, mass, volume or surface area. For a product of SIP value 1, when the average bioburden of a product is greater than or equal to 1.0, it is recommended to use the entire product for sterilization validation. But in some cases, it is not feasible for large medical devices to be used in full for sterilization validation. In such cases, the largest portion of the product should be selected. For products of SIP value 1 and average bioburden less than 1.0, it is always recommended to use the entire product for validation. If the bioburden is evenly distributed across the item, any portion can be considered as SIP, and in case of uneven distribution, the portion of the product that presents the highest challenge shall be used as SIP. Care has to be taken to make sure that no additional bioburden is added to the SIP while preparing and placing the SIP for sterilization validation. It is recommended to prepare SIP in environmentally controlled conditions using the same non-irradiated material to prevent additional bioburden and to simulate the final product. Non-irradiated SIPs are validated using the test of sterility in a way that 17 of the 20 SIPs should show a positive test of sterility (i.e. presence of microorganisms in a microbiological test) before irradiation and the same products will be again subjected for the test of sterility after irradiation with verification of the selected dose. Tests of sterility experiments are usually performed using soybean casein digest broth.

5 Determination of Sterilization Dose

Once the material for sterilization is ready, the challenge is to identify and standardize an irradiation dose appropriate for the material. The dose setting methods were originally developed by Tallentire and subsequently modified as per requirement. The method determines the probability of having a surviving microorganism after irradiation in comparison to the initial number of microorganism prior to irradiation. A sterilization dose for a product means the minimum dose that can be used for irradiation for attaining a definite sterility assurance level (SAL). SAL as defined in ISO document is the "probability for having a viable microorganism being present on a product unit after sterilization". This suggests that the probability of identifying a microorganism on the material irradiated with this specific dose should be one in one million units tested or 10^{-6}. To reduce the harm created by the absorbed dose of radiation by the material, it is necessary to understand the bioburden on the material prior to sterilization. This subsequently allows control of the radiation dose proportional to the bioburden. The current methodologies for determining the radiation dose depend on the natural bioburden present on the material which is evaluated by a series of test of sterility experiments performed in a standard microbiology laboratory before and after irradiation. Once the bioburden is identified, the reference table provided by ANSI/AAMI/ISO 11137 standards may be followed to set appropriate applied dose in kilogray (kGy) corresponding to the intensity of bioburden. This is considered as the reference SAL or verification dose. Verification dose according to ISO is defined as the "radiation predicted to give a predetermined SAL

greater than or equal to 10^{-2} used in establishing the sterilization dose". Dose setting experiments should be carried out in an irradiator calibrated for its performance according to ISO 11137-1.

5.1 Based on Bioburden Information

This method uses the bioburden data collected from the product to determine the sterilization dose. A reference table to determine the sterilization dose values for various products by determining their bioburden and the standard distribution of resistance of the microorganism corresponding to the bioburden is projected. The standard distribution of resistance values is described in terms of the decimal reduction dose (D_{10}) values. D_{10} values as defined by ISO are the radiation doses (kGy) required to kill 90% of the total number of microorganisms present on the product by irradiation. The reference table provides the values for verification and sterilization dosages required to achieve the sterility assurance level of 10^{-2}, 10^{-3}, 10^{-4}, 10^{-5} and 10^{-6} for a given value of Standard Distribution of Resistances (SDR) based on its bioburden. The dosage value required to achieve a SAL of 10^{-2} is considered as the verification dose, and the dosage value required to achieve a SAL of 10^{-6} is considered as the sterilization dose.

Bioburden is usually calculated for individual products, and in case the bioburden is low per product, multiple products can be pooled to determine the average bioburden per batch, called the batch average bioburden. Multiple batches can also be pooled to form overall average bioburden. If batch average bioburden is higher than overall average bioburden, the highest value for batch average bioburden will be used to determine verification dose and vice versa if an overall average bioburden is high. A minimum of 100 products will be subjected to irradiation with the verification dose for validation. The highest dose to the product shall not exceed 10 % of the calculated verification dose. After which, a sterility test is performed on each irradiated product to determine the presence of microorganisms. If in case more than three products showed the presence of microorganism on the test of sterility experiment, then the verification dose has to be recalculated. If in case the verification dose is acceptable, then the sterilization dose is calculated from the reference table, the dose value corresponding to a SAL of 10^{-6}.

5.2 Determination of Dose by Fraction Positive Information from Incremental Dosing

This method provides a more homogenous D_{10} value based on the bioburden of the products to be sterilized. In this method, bioburden is evaluated post-exposure of products to a series of an incremental dose of radiation followed by the test of

sterility. That particular dose in which 99% of the products (99 out of 100) are negative for the test of sterility or are sterile will be considered as the verification dose. This dose is expected to achieve a sterility assurance level (SAL) of 10^{-2} when used for irradiation of the products. There are two different approaches to determine the sterilization dose by incremental dosing method. First one is a general method applied in most cases and the second method is applied in case of products with low bioburden.

In the first method (method 2A), 20 products from each of the 3 batches will be subjected to irradiation using 9 incremental doses starting from 2 kGy with an increment of 2 kGy. The dose at which only 1 out of 20 products was shown negative for the test of sterility is considered as the first fraction positive (FFP) dose. The median average of all the FFPs of the three batches is used to calculate the first fraction positive (FFP) dose. The first immediate dose in the increment series that will provide a negative test of sterility for all the 20 products in all the 3 batches will be considered as the dose that will be used for calculating the verification dose and designated as d*. If the highest value of estimated dose (d*) of any individual batch differs by a value of less than 5 kGy to the median average of all the three batches, then the median average d* value is considered as the estimated verification dose (D*) that will provide a sterility assurance level of 10^{-2}, or else if the difference is equal to or more than 5 kGy, the d* value of the highest batch is considered the estimated verification dose (D*).

For evaluation of the verification dose setting, 100 products from the batch that has almost same d* and D* value are selected. The selected batch is designated as CD* batch. These products from the selected batch will be irradiated by the estimated verification dose (D*) with a maximum deviation of 1 kGy. D* is the initial estimate of the dose that will help the product to achieve a SAL of 10^{-2}. Post-irradiation these products will be subjected to the test of sterility and the number of positives is counted and is designated as CD*. The highest dose delivered will be considered as the estimated dose and is designated as *DD**. If the CD* values fall within 1 to 15 and the irradiation dose employed does not exceed the estimated verification dose by 1 kGy, then the dose values are accepted as verification dose that will achieve a SAL of 10^{-2}. The first no positive (FNP) dose is then calculated based on the CD* values which is the number of positives for the test of sterility experiments. An additional 2 kGy dose is added to the highest dose values (DD*) proportional to the increase in the number of positives in sterility test experiments as mentioned in ISO standards.

To establish the sterilization dose, the estimated D_{10} dose values (DS) will be required to achieve inactivation of 90% of a microbial population present on the product. DS values are calculated from the FFP (first fraction positive) dose and the first no positive (FNP) dose as follows:

$$\mathrm{DS} = 2 + 0.2\left(\mathrm{FNP} - \mathrm{FFP}\right), \text{where} \left(\mathrm{FN} - \mathrm{FFP}\right) \text{is less than 10 kGy}$$

$$\mathrm{DS} = 0.4\left(\mathrm{FNP} - \mathrm{FFP}\right), \text{where} \left(\mathrm{FNP} - \mathrm{FFP}\right) \text{is greater than or equal to 10 kGy}$$

Further, the final estimate of the verification dose is calculated as per the equation:

$$D^{**} = DD^{*} + \left[\log\left(CD^{*}\right)\right]\left(DS\right)$$

The sterilization dose is then calculated based on the formula

$$\text{Sterilization dose} = D^{**} + \left[-\log\left(SAL\right) - \log\left(SIP\right) - 2\right]\left(DS\right)$$

where:

D** is the final estimate of the dose that will provide a 10^{-2} SAL
SAL is the preselected sterility assurance level
SIP is the portion of the product (sample item portion) used for determining D** and DS
DS is an estimate of the dose required to inactivate 90 % of the microorganisms

The second method (method 2B) for sterilization dose estimation using fraction positive information from incremental dosing uses the first method (2A) with minor modifications. In method 2B, the entire product is used for the dose determination process where the SIP is equal to one. In this method, a series of eight doses are utilized starting from 1 kGy with an increment of 1 kGy. The highest dose delivered at each increment should not exceed 10% or 0.5 kGy of the estimated increment. The rest of the protocol remains the same for both the methods. The first no positive (FNP) dose in the method 2B experiment does not exceed 5.5 kGy.

The sterilization dose is then calculated as follows:

$$DS = 1.6 + 0.2\left(FNP - FFP\right)$$

$$\text{Sterilization dose} = D^{**} + \left[-\log\left(SAL\right) - 2\right]\left(DS\right)$$

where:

D** is the final estimate of the dose that will provide a 10−2 SAL
SAL is the preselected sterility assurance level
DS is an estimate of the dose required to inactivate 90 % of the microorganisms surviving DD*

5.3 Determining Sterilization Dose by VDmax: Substantiation of 25 kGy or 15 kGy as the Sterilization Dose

This method of substantiation of sterilization dose is also based on the determination of bioburden to establish the verification dose and thereby the sterilization dose. This method is employed to those products whose batch average bioburden is

less than or equal to 1000 CFUs per product. The verification dose experiment is conducted on ten products or portions of it, and the dose required to attain a SAL of 10^{-1} is determined. In case of products with an average bioburden of 0.9 and below, the entire product will be used for verification dose determination, and in case of products with bioburden above 0.9, SIPs can be used.

To perform the verification dose experiment, bioburden of individual products is determined along with the overall average bioburden and the batch average bioburden. If the highest bioburden value is more than two times the difference between the batch average bioburden and overall bioburden, the determined highest value for bioburden is used for further determination of the verification dose. Based on the bioburden values obtained, a reference table is provided in the ISO standards to calculate the corresponding values of $VDmax^{25}$ and SIP dose reduction factors for levels of average bioburden less than or equal to 1000 CFU.

The formula for calculating VDmax is as follows:

$$\text{SIP VDmax}^{25} = \left(\text{SIP equal to 1.0 VDmax}^{25}\right) + \left(\text{SIP dose reduction factor} \times \log \text{SIP}\right)$$

The estimated verification dose obtained (SIP $VDmax^{25}$) is used to perform the verification dose experiment using ten products from each batch that was used to determine the estimated bioburden. After irradiation of these products by the verification dose, a test of sterility is carried out on the irradiated product. If only one product per ten irradiated products is found to be positive for the test of sterility experiment, the $VDmax^{25}$ value is accepted, in case of two positive results, a confirmatory verification dose experiment is conducted, and in case of three, the dose is rejected. For $VDmax^{25}$ determination for a single batch, ten products from the batch are used, and in case the bioburden is low, more products are pooled.

In cases where the batch average bioburden of product is less than or equal to 1.5, a different substantiated dose of $VDmax^{15}$ is used. $VDmax^{15}$ dose substantiation is usually performed for irradiation of entire product item (SIP = 1). The procedure to be followed in general is similar to the determination of $VDmax^{25}$ values. The average burden estimated will be used to obtain the $VDmax^{15}$ dose values, from the reference table provided in ISO standards for determining $VDmax^{15}$ dose levels for products of average bioburden less than or equal to 1.5. In both cases of substantiation of 25 kGy or 15 kGy as the sterilization dose, alternate sterilization methods have to be employed if more positive test of sterility experiments is reported both in performance of verification dose experiment and in the confirmatory verification dose experiment.

6 Sterilization Dose Audits

After establishing the sterilization dose for the products to be irradiated, it has to be ensured that the performance of the irradiator and the dose delivered meet the requirements of irradiation. This is ensured by frequent and periodic audits where the irradiator meets the operational requirements and also the dose delivered is

equivalent to the dose calculated for irradiation of the particular product. In a sterilization dose audit, the above-mentioned methods are followed to reverify the procedure and the recorded results. A sterilization dose audit generally contains the following steps:

- Obtain details of the product.
- Determine the average bioburden.
- Perform the verification dose experiment.
- Interpretation of results.

While performing the test of sterility experiment for the interpretation of results, if no more than two positive tests of sterility are obtained, the sterilization dose audit is accepted. If three or more positive tests of sterility are obtained in a sterilization dose audit and the results cannot be ascribed to the incorrect performance of tests of sterility or incorrect delivery of the verification dose, then the sterilization dose might be inadequate, and immediate steps to augment the sterilization dose should be established.

7 Dosimetry and Dosage Measurement

Dose measurement is another integral part of the validation for radiation sterilization. Appropriate dosage measurement should be done at all stages of the sterilization process, such as development, validation and routine observations abiding both the national and international standards. Measurement of radiation dose can either be direct or indirect. A direct dose measurement would be from the location of interest, and if the location is remote, the measurement can be done using factors determined during the operational and performance qualification studies.

7.1 Dosimetry System Selection and Calibration

Dosimetry and dosimetry systems are detailed in ISO 11137-3: 2017, “Sterilization of health care products—Radiation: Guidance on dosimetric aspects of development, validation and routine control”. The dosimetry system used in the development, validation and routine observation of the process of radiation sterilization should provide both accurate and precise measurements over a broad dose range. This accuracy should sustain under all the conditions of use so far mentioned in the ISO. It is possible that different dosimetric systems require dose ranges that differ in the process of either development of radiation sterilization or validation or routine observation. Dosimeter system should be well-calibrated and the interpretation of its readout should be well supported by data. Another important aspect is the presence of competent and trained staff to handle both the calibration and operation

of the dosimetric systems which requires special skill and mandatory training. The dosimeter build-up cost should be reasonable and non-toxic in nature. Additionally, the measurements of absorbed dose for sterilization of healthcare products are done with the placement of water as the background. Thus all calibration of dosage measurement needs to be done using water. The calibration of measurement traceability for both direct and indirect measurements can be defined as the best estimate of dose for the respective dose measurements.

7.2 Calibration of Dosimetric Systems

Calibration is the most important part of the dosimetric assessment and should be done prior to the actual measurement. Dose measurements are dramatically influenced by external factors such as relative humidity, temperature, exposure to light, rate of irradiation and time between irradiation and measurement. Variations among different batches of dosimeters with respect to their response to different external factors are mentioned above. Thus, it is imperative to calibrate the dosimeters in the actual conditions that the measurements are planned to be taken and every time a new dosimeter is used. The calibration curve supplied by the dosimeter manufacturer is useful to understand the expected response of dosimeter, but it should not be used as the standard, and its validity should first be verified. The dosimeter should be calibrated in the presence of the irradiator being used and not from the irradiation carried out by a different irradiator.

The calibration irradiations and reference standard dosimeters should be supplied by a national authority on standards with a calibration certificate to ensure traceability of dose measurements. The accurate dose measurement also requires the calibration and consistent performance of other parts of the dosimetry system. Thus all the equipment and instruments associated with the dose measurement system need to be calibrated, or their performance should be tested. It is also important that the calibrations remain valid for some specific period, and to maintain this validity, the calibration is verified using the set reference dosimetry system at periodic intervals. If there is a significant deviation from the set calibration due to change in the source of the radiation or its reduced performance, this should be rectified immediately. Variations in the environmental factors such as temperature and humidity can also affect the dosimeter response which demands its periodic check.

The dosimetric systems are also known to be influenced by the period between the time of termination of irradiation and the subsequent measurement. The extent of this influence can depend on the way the dosimetric system is stored. Immense care should be taken while storing the dosimetric systems, and the effects of the vagaries of nature should be avoided, or if unavoidable, these uncertainties or deviations should be taken into account.

7.3 Uncertainty in Dose Measurement

As previously discussed, the dose measurements should be traced back to an authentic and credible national or international authority on standards, and the level of uncertainty should be known. All potential sources of measurement uncertainties or standard deviations should be noted and their magnitudes should be evaluated. To make things easier and faster, measurements on the combination of uncertainties may be accounted than assessing them individually. Both direct and indirect types of measurements require an estimate of uncertainties or standard deviations. This is since measurements from a dosimeter on the same instrument would give a scatter of values as multiple factors affect the response of the dosimeter. These factors can depend on the dosimeter used, the skill of the operator or the environment. Thus it is important to know the uncertainties and the parameters under which they exist. As discussed earlier, the dose measurement is the best estimate of the true value of the absorbed dose by the products, but due to inherent uncertainties in the measurements, the true value of the absorbed dose would either be less or more of the dose measurement. The dose measurement follows a normal distribution with a Gaussian curve, with the peak of the curve being the best estimate value. As with all Gaussian distributions, the values lying before and after the peak become increasingly less probable, with the width of the curve being the standard deviation (sigma, σ). As mentioned above, it is important to identify all potential sources of uncertainty while measuring dose followed by their individual or combination quantification. Each component of the uncertainty is then assigned an effective standard deviation, and all the standard deviations are combined to produce an estimate of overall uncertainty. Since an overall uncertainty comprising both random and systemic influences is obtained, it provides a quality of the measurement of dose. An "uncertainty budget" represents the tabulated form of individual forms of uncertainties, their values and the method of estimation.

In the case of dose measurements in radiation sterilization, the uncertainty is associated with the direct or the indirect method of measurement. The uncertainty components of the direct or the indirect ways of dose measurement in an irradiation container are as follows. Given below is not a checklist but is a guideline to establish the uncertainty budget:

- The uncertainty reported by the calibration standards laboratory
- The uncertainty that arises due to the mathematical fitting of the calibration function
- The uncertainty that is related to the effect of environmental factors that influence dosimeters during calibration and usage
- The uncertainty related to the reproducibility factor of the dosimeter
- The uncertainty for indirect measurements derived from dose mapping
- The uncertainty that arises from variations in the irradiator dose delivery between the irradiation of the dosimeter and the irradiation of the container where the dose is measured from

7.4 Establishing the Maximum Acceptable Dose

To conduct tests establishing maximum acceptable dose, products that have been irradiated to doses that are equal or greater than the highest anticipated dose should be utilized for the sterilization procedure. Here again, the true estimate of the maximum dose received during the sterilization procedure is influenced by the features of the irradiator and the loading pattern of the product. This true value of maximum dose changes if the irradiator or the loading pattern of the product changes. Further, the surface properties of the product used should be studied carefully to ensure that the dose is determined accurately and that the dose distribution is uniform throughout the surface of the product. Care should be taken about the interpretation of test results and assignment of the maximum acceptable dose. This is because the product used for establishing the irradiation doses is tested for a range of doses and the maximum acceptable dose is the lowest dose received by the product for which the properties were found to be acceptable. It is also possible that the maximum acceptable dose lies out of the calibrated range of the available dosimetry systems. In such times, the dose can be delivered in increments while monitoring each dosage. The final, total dose is the sum of these incremental doses. However, incremental doses would have its side-effects of either being inefficient or changing the performance of the product.

7.5 Establishing the Sterilization Dose

The method of establishing the sterilization dose depends on the product to be irradiated within a dose limit that specifies tolerance. There should be no compromise on the outcome of the dose establishment method, where the dosimetry system should be adequately accurate and precise to ensure that the dose measurements are within the limits of the tolerance specified by this method. The achievement of doses in the tolerance limit is based on the measurements used to arrive at the minimum and the maximum dose for the product at any given point. It is also important to configure the product during irradiation to achieve minimum variation in dose, both individually and between product items. In some cases, it may also be required to disassemble and repack the product to achieve the acceptable distribution of the doses on the product. The product bioburden might get affected due to dismantling and repackaging of the product. Detail mapping of dose for individual products would be required especially in the case of electron beam irradiation. While dose mapping, it may not be necessary to have the same doses as those used during sterilization. By using different doses, the dosimetry system gets enabled to be more accurate in its operating range and thus improving the overall accuracy of the dose mapping. Simultaneously, it is also important that the different doses do not alter the dose distribution for the product. Even here, to obtain and reduce measurement uncertainties of dose to products, multiple rounds of dose mapping exercises need

to be performed on the mentioned product. If not, multiple dosimeters should be placed in the irradiation container to identify the locations of and measure the limits of the doses. The measurement uncertainty thus obtained should be taken into account while performing irradiations for sterilization to ensure that the specified doses of tolerance are met.

For usage of gamma rays for irradiation, the special irradiator is designed for irradiation at lower doses than the sterilization dose or a defined location such as on a turntable or a special irradiation pathway designed for low dose irradiation. For electrons or X-rays used for irradiation, lower doses can be achieved by reducing the irradiator beam current, increasing the speed of the conveyor or reducing the product residence time in the beam. Extreme care should be taken while determining the beam parameters to obtain low doses for sterilization. For example, in some electron accelerators, changing the beam current might change the electron energy, thus affecting the dose distribution. For irradiation using the electrons, the product can be covered by the material to scatter the electrons and produce a more dose distribution. The surrounding material should be characterized with its known nature. X-ray irradiations and their unidirectional beam may produce high doses of irradiations, which might affect the product performance. In this case, too, the product can be surrounded by some material that leads to a uniform distribution of X-ray irradiation.

7.6 Installation Qualification

This section demonstrates the supply and the installation of the irradiator according to its specifications. The characteristics of the beam for an electron or X-ray irradiator should also be determined. This includes the respective energies, average beam current, scan width and scan uniformity. The details of the characterization depend on the design and the construction of the irradiator. The methods involved in determining the electron beam features involve dose measurement traceable to a national or international authority on standards. During the installation qualifications, it is required to measure either the electron beam energy or the X-ray energy. Wherever the design of the X-ray irradiator permits, it is normal to measure the electron beam energy incident on the target in accordance with the standard methods. Whereas for electron accelerators the beam is scanned and its pulse is taken, there should be sufficient overlap between the pulses and the scans to provide the required dose uniformity on the product surface. The relationship between several parameters of the electron beam such as the scan frequency, scan width, pulse repetition rate and the conveyer speed relative to the cross-sectional distribution of the unscanned electron beam at the surface should be considered. In the case of gamma irradiators, there are no such dosimetric requirements. Depending on the irradiator specified, it is necessary to carry out the dose measurements and/or dose mapping in the installation qualifications. This is to verify that the operation is within specifications of dose rate and dose uniformity.

7.7 Operational Qualification

After successful installation of the irradiator, the purpose of the OQ is to demonstrate the operational capability and deliverance of appropriate dosage within defined acceptance criteria. This can be achieved by determining the dose distributions and dose magnitude by dose mapping exercises and further relating these dose attributes to process parameters. A crucial part of the OQ is repeated measurements to show consistent and stable operation and should be performed at specified intervals. Following any change that might affect the dose or dose distribution, such as source replenishments in the gamma facilities or modifications to conveyor systems, it is all the more important to have repeated measurements of the dose. The strategy for OQ should be based on the anticipated methods of operation of the irradiator.

7.8 Dose Mapping for Gamma Irradiators

The irradiator can be characterized with respect to the distribution and reproducibility of the dose in defined loading configurations. Similarly, to establish the effect of process interruption on the dose throughout the container, dose mapping should be done by placing the dosimeters in the irradiation containers filled with a material of homogeneous density up to their design limits. These materials can be sheets or plates of expanded polyethylene foam, cardboard or wood. Two such dose mapping exercises should be carried out, one with a material of lower density, the density at which the irradiator is planned to be used, and another with a material of higher density fitting the range. As discussed earlier for PQ, OQ should be done for every pathway through the irradiation container. The relationship between the irradiation time and the minimum dose is non-linear in the case of gamma irradiator units. In such a case, more than two dose mappings over a range of different densities are required to determine the performance characteristics. At least three irradiation containers should be used to map the doses for each chosen density to allow determination of variability of dose and dose distribution within and between containers. For a new irradiator, a greater number of replicate exercises would be required for dose mapping.

During dose mapping, separate dosimeters, dosimeter strips or dosimeter sheets should be placed within the irradiator container in sufficient quantity to determine dose distribution. The number of dosimeters to be placed depends on the size of the irradiation container and the design of the irradiator. For requalification purposes, the data from earlier exercises can be used to optimize the positioning of the dosimeter, so that the dosimeters can be focussed in the areas of potential minimum and maximum dose and high dose gradients. What can be useful in optimizing the positioning of the dosimeters and reducing the number of dosimeters is mathematical modelling techniques with appropriate benchmarks. Thus data obtained from OQ dose mapping exercises can be used to establish materials of different densities, the

relationships between timer settings, conveyor speed and the dose magnitude at a defined location within the container. Another correlation that can be established would be between the dose uniformity within the irradiation container and the material density. Approximations of these relationships can be supplied by the irradiator manufacturer or as suggested earlier can be obtained by calculation using mathematical models. These calculations obtained through mathematical modelling can be used to refine the approximate values provided by the manufacturer.

Process interruption is an important aspect of operational qualification. It causes a change in magnitudes of the minimum and maximum doses and also the place at which these extremes occur. Thus, it becomes important to assess the effect of process interruption on dose throughout the irradiation container. Here, specific dose measurements can be carried out using a container having dosimeters located in areas which are expected to be most influenced by source and are interrupted when the container is close to the source. This effect of process interruption is assessed by comparing the results with those where the dose mapping exercises were carried out under normal process conditions. Here again, mathematical modelling and follow-up calculations can help in understanding the process interruption.

Dose mapping should be performed for special conveyor systems or fixed locations in the irradiator designated for manually placing the products. The product present in the main irradiator pathway may also influence the dose distribution at the above locations. Considerations should thus be given to the effect on the calibration and uncertainty associated with the use of such conveyors and locations with respect to dose rate or temperature. A dosimetry system calibration might be established for each irradiator pathway and a fixed location, generating a new calibration curve.

The dose mapping in performance qualification (PQ) can be reduced by determining the effects of partially filled irradiation containers and loading of the product in the centre of the container towards the purpose of achieving desired dose uniformity ratio. The density of the processed product can have effects on the magnitude and distribution of dose. An acceptable range of densities that can be processed together based on the results obtained from the dose mapping exercises should be available. The design of the irradiator and how density changes are introduced in the irradiator can also affect the dose magnitude and distribution. This density should fall in the range of densities that are processed routinely. Dose mapping results from an irradiator which faces changes in densities when compared to those containers where there has been no change in density.

7.9 Dose Mapping for Electron Beam Irradiators

Dose mapping should be carried out for the energy of the beam irradiator used for product irradiation**.** In case more than one energy or scan width is being used, then the OQ dose mapping should be carried out for each energy and scan width to cover the operational limits used for product irradiation. Similar to the procedure followed

for gamma radiators, only one density should be used for OQ in the electron beam irradiators, but more detailed information can be obtained by using more than one density and single-sided irradiation, with densities being within the limits of the density range for which the irradiator is intended to be used. By using single-sided irradiation, maximal information about the consistency and stable operation of the irradiator can be obtained. Below are the OQ followed for electron beam irradiators.

Electron beam irradiators are designed in such a way that the containers are conveyed through the radiation field with or without separation between the containers. This can be done by:

(a) Designing fixed spacing between containers that results in irradiation of only one container by the field radiation at a time
(b) When the product batches are changed
(c) When the radiation parameters are changed

The spacing, differences in the densities or material configurations between the containers play an influential role in the dose distribution within each container. Therefore, dose mapping carried out to examine such effects gives information that is useful for PQ dose mapping.

During dose mapping, separate dosimeters, dosimeter strips or dosimeter sheets should be placed within the irradiator container in a three-dimensional array, including the surface. The number of dosimeters to be placed depends on the size of the irradiation container, the design of the irradiator and the energy of the electron beam. For requalification purposes, the data from earlier exercises can be used to optimize the positioning of the dosimeter, so that the dosimeters can be focussed in the areas of potential minimum and maximum dose and high dose gradients. What can be useful in optimizing the positioning of the dosimeters and reducing the number of dosimeters is mathematical modelling techniques with appropriate benchmarks. Thus data obtained from OQ dose mapping exercises can be used to establish electron beam irradiators, the relationships between features of the beam, conveyor speed and the dose magnitude at a defined location within the container. Process interruption is an important aspect of operational qualification. It causes a change in the magnitude of the minimum and maximum doses and also the place at which these extremes occur. This effect can be determined by using dosimeters at the places where the effect of process interruption is the greatest. The effect of process interruption should be assessed for different irradiation conditions and different causes of interruption. The effect can vary at high conveyor speed with high mass product and low conveyor speed with low mass product, for example. Interruption occurring from the safety system, from the electron beam and from the conveyor might have different effects on dose which should be assessed. In routine processing, the allowable number of interruptions that can occur without doses to the product falling outside the specification should also be considered.

The above dose mapping practices for electron beam irradiators need to be carried out for operational qualification for the X-ray irradiators.

7.10 Performance Qualification

There are several factors related to the product and irradiator that influence the distribution of dose on the product. Dose mapping exercise in PQ generates important data which can be used to identify locations and magnitude of both minimum and maximum doses to the product. Dose mapping should be carried out scrupulously to identify the magnitudes and locations of the minimum and maximum doses on or in the product that is being irradiated. This can be used to calculate the relationship between these doses and the dose at the routine monitoring positions. This can also be useful in determining the values for process parameters, such as timer setting or conveyor speed which calibrated to meet the specified sterilization dose without going beyond the maximum acceptable dose. As discussed in the earlier section, information obtained from the OQ dose mapping can provide the initial information required for the placement of dosimeters for the PQ dose mapping. PQ needs to be repeated if OQ measurements show that there is some variation with the PQ measurements due to changes in the irradiator or the product. Otherwise, there is no need to repeat the PQ on a regular basis.

Performance Qualification for Irradiators

During dose mapping, individual product carton is arranged within an irradiation container in such a way that defines the intended routine loading pattern. Key product characteristics such as carton dimensions and weight, allowable variations in these parameters, the dose specifications for the product and details obtained from OQ dose mapping should be considered. Products with low density tend to be homogenous so that the orientation of individual products within the irradiation container does not have a significant effect on dose distribution when irradiating with gamma rays. But for non-uniform products with high-density components and void spaces, a specific orientation of products might be required within each irradiation container. If the product can move within the product carton, then several possible orientations of the product within the carton should be used for dose mapping, and a worst-case scenario should be established with respect to dose distribution.

7.11 Dosimetry Placement

Dosimeters should be placed in an irradiated container and should be mapped in sufficient numbers to determine the minimum and maximum dose locations. Data obtained from the OQ dose mapping might be used to guide the placement of the dosimeter, focussing the dosimeter on expected locations. The dosimetry system should have a high spatial resolution that allows measurement of dose gradients that might occur at the material interfaces. Some products can cause localized shielding

or scattering; it might get necessary to use thin film dosimeters to obtain the required spatial resolution. For irradiation of low-density products by gamma rays, it is appropriate to place the dosimeters outside the sterile barrier system of the product. For example, products made up from low atomic number elements do not contain material with densities or masses enough to cause local shielding or scattering to other areas. Otherwise, for denser materials, it is advised to place the dosimeters inside the sterile barrier system of product to determine the minimum and maximum doses. For example, an implant made from titanium has a higher density as compared to the packing material and therefore would require placement of dosimeters inside the sterile barrier system.

7.12 Replicate Dose Mapping Exercises

Variability in measured doses can occur due to irradiator variation, product variation and dosimeter reproducibility. These variations then require replicate dose mapping exercises, at least three, to obtain more information. A separate irradiation container is recommended to be used for dose mapping to obtain statistically valid data. For such replicate exercises, it could be sufficient to place dosimeters only in areas of dose extremes.

7.13 Analysis of Dose Mapping Data

Dose mapping data are analysed such that:

(a) A routine monitoring position related to the locations of minimum and maximum doses to product is defined
(b) The components of uncertainty related to the use of routine monitoring position to make indirect measurements are defined

7.14 Routine Monitoring and Control

The measurement of dose at the routine monitoring position during processing is used to verify that the minimum dose is equal to or more than the sterilization dose and that the maximum dose does not exceed the maximum acceptable dose. These acceptable doses are given in the process specification. Both types of dose measurements, direct and indirect, represent the best estimate of dose for product conformity. Thus, values from dose measurements should not be corrected by uncertainty measurements associated with it.

7.15 Frequency of Dose Measurements

The measurement of dose at the routine monitoring position provides process information that is independent of any other control or measurement system of the irradiator. The frequency of dose measurement should be chosen based on the features of the irradiator and other processes. The amount of product that might be discarded following an out-of-specification dose measurement could also be an important consideration in setting this frequency.

For gamma rays, electron beam or X-rays-mediated irradiation, dosimeters are typically placed at the beginning and end of each run of a product including a particular category. Also, the dosimeters should be placed such that at least one dosimeter is within the irradiator at all times. Plotting of all routine dosimetry measurements on a chart provides valuable information on the overall performance of the irradiation process. This enables taking appropriate preventive actions before any out-of-specification measurements occur. This approach can also be extended to full statistical process control.

8 Conclusion

This chapter is to provide an overview of recommendations from ISO for installation and process validation of sterilization of medical devices by employing radiation. However, for any use of the relevant content, it should be referred back to the ISO standard guidelines 11137. Compliance with these requirements for the process of radiation sterilization ensures that the process followed is reliable and reproducible with a reasonable level of confidence. ISO 11137 should be part of the quality management of all organizations performing radiation sterilization to ensure their quality of sterilization. These guidelines and regulations will bring in similar standards for radiation sterilization process across the globe.

References

ISO 11137-1:2006, Sterilization of health care products — Radiation — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices.

ISO 11137-2, Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose.

ISO 11137-3, Sterilization of health care products – Radiation – Part 3: Guidance on dosimetric aspects of development, validation and routine control.

ISO 11737-1, Sterilization of medical devices — Microbiological methods — Part 1: Determination of a population of microorganisms on products.

ISO 11737-2, Sterilization of medical devices — Microbiological methods — Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process.

ISO 13485, Medical devices — Quality management systems — Requirements for regulatory purposes.

ISO 10993-1:2003, Biological evaluation of medical devices — Part 1: Evaluation and testing.
ISO 10012, Measurement management systems — Requirements for measurement processes and measuring equipment
ISO/ASTM 51608, Practice for dosimetry in an X-ray (Bremsstrahlung) facility for radiation processing
ISO/ASTM 52303, Guide for absorbed-dose mapping in radiation processing facilities
ISO/ASTM 51261, Practice for calibration of routine dosimetry systems for radiation processing
ISO/ASTM 52701, Guide for performance characterization of dosimeters and dosimetry systems for use in radiation processing
ISO/ASTM 51707, Standard guide for estimation of measurement uncertainty in dosimetry for radiation processing
ISO/ASTM 51649, Practice for dosimetry in an electron beam facility for radiation processing at energies between 300 keV and 25 MeV
ISO/ASTM 52628, Standard practice for dosimetry in radiation processing
Tallentire A. Aspects of microbiological control of radiation sterilization. J. Rad. Ster. 1973,1 pp. 85–103.
Tallentire A., Dwyer J., Ley F.J. Microbiological control of sterilized products. Evaluation of model relating frequency of contaminated items with increasing radiation treatment. J. Appl. Bact. 1971, 34 pp. 521–34
Tallentire A., & Khan A.A. The sub-process dose in defining the degree of sterility assurance.
In: Gaughran, E.R.L and Goudie, A.J. (eds.), Sterilization by ionizing radiation, Vol. 2. Montreal: Multiscience Publications Ltd., 1978, pp. 65-80
Kowalski J. et al. Field evaluations of the VDmax approach for substantiation of a 25 kGy sterilization dose and its application to other preselected doses. Radiat. Phys. Chem. 2002, 64 pp. 411–416
Kowalski J., & Tallentire A. Aspects of putting into practice VDmax. Radiat. Phys. Chem. 2003, 67 pp. 137–141
Kowalski J., & Tallentire A. Substantiation of 25 kGy as a sterilization dose: A rational approach to establishing verification dose. Radiat. Phys. Chem. 1999, 54 pp. 55–64
Kowalski J., Aoshuang Y., Tallentire A. Radiation sterilization — Evaluation of a new method for substantiation of 25 kGy. Radiat. Phys. Chem. 2000, 58 pp. 77–86

ISO 11135: Sterilization of Health-Care Products—Ethylene Oxide, Requirements for Development, Validation and Routine Control of a Sterilization Process for Medical Devices

Indumathy Jagadeeswaran and Sunitha Chandran

1 Introduction

Medical devices produced under standard manufacturing conditions might have microorganisms on them, and these microbiological agents should be decontaminated in accordance with quality management systems (ISO 13485) and thereby transform the non-sterile medical devices into sterile ones suitable for its intended clinical use. Ethylene oxide (EO) is used as a sterilizing agent for heat and moist-sensitive medical devices. EO is a colorless gas that is toxic, flammable, and explosive and requires caution during its usage and handling. Sterilization achieved by EO can be best described by the exponential relationship between the extent of EO treatment and surviving microorganisms on a medical device. To ensure appropriate microbicidal activity of EO and sterility of medical devices, compliance with the requirements of ISO 11135 is recommended, which has been discussed in this chapter. The specifications of this standard vary from country to country (refer EN 556-1 and ANSI/AAMI ST67) by discretion of the regulatory authorities. Though ISO 11135 has grouped together and presented the activities required in sequential manner, ISO 11135 does not require these activities to be performed in the same order mentioned. It also does not specify the activities to be carried out by individual or organizations, considering the involvement of number of separate individuals and/or organizations in the accomplishment of sterilization processes.

I. Jagadeeswaran (✉)
Department of Biological Sciences, Southern Methodist University, Dallas, TX, USA

S. Chandran
SCTIMST TIMed, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_9

2 Selection of Sterilization Process

Selection of a suitable sterilization process and tolerance level is of utmost importance for the normal functionality of the medical device. Factors such as material property, design characteristics, packaging, loading configuration and compatibility with EO, are to be considered for selection of an appropriate sterilization process. In health-care facilities, efficacy of sterilization process adopted can be influenced by several factors such as sterilization equipment availability; attainment of specific conditions by the equipment; sterilant to be used (100% EO or EO mixed with diluent gases); its concentration; tolerance level of the physical parameters like temperature, humidity, pressure, etc.; residual amount of EO and/or its reaction products; and outcome of process development.

Sterility assurance level (SAL) is the probability of a single microorganism to remain viable, post-sterilization. Bioburden is one of the most commonly used parameters to assess SAL. The location within the medical device, where sterility is most difficult to achieve, might have reduced sterilant penetration and thereby be more likely to have significant amount of bioburden. Therefore, the aspects to be considered for appropriate placement of biological challenge and achievement of the required SAL include length and inner diameter of lumens, diffusion efficiency of EO, absorbance of both the product and material, load configuration, and size. To ensure that sterilization process continues to meet or maintain the required SAL, any changes to the equipment, process, product, and packing should be evaluated and noted.

The number and types of microorganism should be monitored as per ISO 11737-1. Selection of appropriate sterilization process is required to achieve the acceptable SAL. An appropriate sterilization process for a medical device is established by use of microbiological testing (cycle lethality tests) and other analytical tools. The standard also recommends that desired storage conditions for EO with specifications like concentration, dilution, and shelf life should be specified and followed. While establishing an appropriate sterilization process, impact of the sterilization process parameters (temperature, time, humidity, pressure changes/rates and EO concentration) and their tolerance on the functionality of the medical device should be assessed.

3 Processing Cycle, Temperature, Time and Pressure

EO sterilization process includes phases such as preconditioning, sterilization cycle, and aeration. Preconditioning the medical devices at a defined temperature and humidity prior to EO exposure helps in controlling the relative humidity of the product and reduces the duration of the sterilization cycle. Sterilization achieved by EO is affected by the moisture content of microorganisms, and low levels of humidity may increase microbial resistance. Conditions or parameters that affect the

microbial effectiveness of sterilization process (i.e., process variables) for preconditioning phase include time, temperature, humidity, and transfer time. Precautions should be taken to maintain temperature and humidity within the desired range throughout the conditioning phase. A maximal time between the preconditioning phase and start of sterilization cycle (i.e., transfer time) needs to be established. Generally, in health-care facilities, optimum transfer time is not more than 60 min.

Sterilization cycle is carried out in a sealed chamber to reduce the viable number of microorganisms on the medical device. Sterilization process includes air removal, chamber leak test, inert gas addition (if applicable), conditioning (if applicable), EO introduction to chamber, specified exposure time to EO, removal of EO, flushing (if applicable), and air/inert gas admission. The process variables for sterilization phase include exposure time, temperature, humidity, EO concentration, and pressure.

Proper aeration is a crucial phase which helps in clearing EO residues from the sterilized product/package. Residues of EO and its reaction products above the specific exposure limits are toxic. EO set points and tolerance levels are outlined in ISO 10993-7. The process variables for aeration phase include time and temperature. Precautions should be taken to maintain a consistent temperature, fresh airflow, and air recirculation in the aeration chamber for reproducible results. Due to the toxic nature of EO and chances of residual amounts to be present on the medical device, it is recommended to maintain material safety data sheet (MSDS) or analogous safety information for the EO concentration or dilutions used. Also precautions for personal health and safety should be specified.

The sterilization process parameters to be established for each phase mentioned earlier include:

(i) Preconditioning room (if used):

  (a) Temperature and relative humidity range
  (b) Time set point and time range

(ii) Sterilization chamber:

  (a) Vacuum and pressure levels and rate of pressure change
  (b) Temperature set point and range
  (c) Humidity control set point and range
  (d) EO and diluent gas (if used) injection pressure set point and range
  (e) EO dwell time
  (f) In-chamber gas flushing setting (if used)

(iii) Aeration room (if used):

  (a) Temperature set point and range
  (b) Time set point and range
  (c) Airflow/changes parameters

Considering the number of establishing parameters, it is impractical to assess the tolerance of all possible combinations of variables. Therefore, process variables

with the greatest impact on the safety and functionality of the medical device and/or its packaging device should be selected and validated. ISO 11135 may be referred for further details. If concentration of EO used for the sterilization process is outside the widely accepted range, microbial effectiveness should be validated. Environmental consequences and measures to be followed to minimize the hazards of EO sterilization, while releasing the product or exhaust, should be identified and documented.

4 Routine Control, Efficacy, and Reproducibility

Periodic monitoring helps in validating specific sterilization process to meet the expected SAL for the sterilized medical device. Routine monitoring ensures that the process parameters specifications have been met for each sterilization cycle. The process challenge device (PCD) is designed to constitute a defined resistance to a sterilization process and is used to assess efficacy of the sterilization process. An external PCD is used for routine microbiological monitoring of production cycles. For routine monitoring and control of the sterilization process, use of internal PCD such as biological indicators (BIs) is commonly preferred. For BIs to be used as part of sterilization establishment process, it shall comply with ISO 11138-2:2017, resistant to EO exposure and placed at an appropriate place in the medical device to pose a challenge equivalent or greater than the challenge posed by the natural bioburden at the most difficult location to be sterilized within the medical device.

Validation includes installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ), and all these validations need to be done prior to testing of the sterilization procedure. IQ ensures proper installation of equipment and its ancillary items as specified for EO sterilization. OQ demonstrates the ability of the equipment to meet the sterilization process variable requirements, and PQ ascertains that the product has been subjected to all the process parameters specified and meets all the requirements to be considered as sterile device. For additional information on the selection, methods used, incubation time, and interpretation of the BIs, ISO 14161 may be referred. Health-care facilities recommend decontamination/cleaning process prior to terminal sterilization for effective and adequate bioburden reduction. The rate of microbiological inactivation provided shall be determined by biological indicator/bioburden and/or the overkill approach.

(a) *Biological Indicator/Bioburden Approach*

Bioburden method combines the knowledge of resistance of biological indicator and the bioburden population for a given sterilization process to establish the sterilization cycle and exposure time. This method is used if the bioburden levels in the medical device are relatively consistent over time and their resistance is equal to or less than the resistance of the BI. The resistance of the internal PCD shall be demonstrated either by time-graded exposures or by population-graded BI exposed to EO. Keeping other parameters constant, lethality of the sterilization process shall be

determined by one of the two commonly used microbiological test methods in accordance with ISO 11737-1 and 11737-2. The first method (direct enumeration) consists of enumeration or physical count of the survivors, and the second method (fraction-negative) uses growth/no growth during fractional cycles.

(b) *Overkill Approach*

Overkill approach is a widely accepted method based on inactivation of reference microorganisms. This method is used if the total inactivation time of bioburden level in the medical device to be sterilized is demonstrated to be less than the total inactivation time of the BI (internal PCD). The sterilization process achieved using this manner is often conservative and use a treatment that exceeds the acceptable criteria to achieve the specified requirements for sterility. Two commonly used methods in this approach are half cycle and cycle calculation approach. The half cycle approach demonstrates total inactivation of the 10^6 challenge BIs at a half cycle exposure time. Cycle calculation method exposes the internal PCDs to the experimental cycle, removing the challenge and testing for survivors, which can be used to calculate the cycle necessary to achieve the required SAL for the medical device. Among these methods, half cycle is most commonly used by medical devices manufacturers and health-care facilities due to its relative ease of use and conservative SAL obtained.

Chemical indicators are also used, but they may not be considered as sole means of establishing sterility. Internal chemical indicators do not assure sterility; they allow detection of procedural errors (i.e., incorrect packing, incorrect loading, or overloading of sterilizer chamber) and equipment malfunctions including inadequate pre-conditioning. If chemical indicators are used as part of sterilization process, they shall comply with ISO 11140-1 and will be used in conjunction with other methods such as microbiological and physical monitoring.

Parametric release method gathers information on physical processing parameters such as chamber relative temperature, humidity, and EO concentration during EO exposure time, to ensure that the sterilization process has been achieved in the medical device, without the use of BIs.

(a) Temperature Measurement

Minimum of two temperature recordings at different locations are to be measured within the sterilizer throughout the sterilization cycle, to ensure that the product is not released as a result of malfunction in temperature sensor. If either of these two readings does not meet the specifications of sterilization process, the load is rejected.

(b) Humidity Measurement

Real-time indication of relative humidity and water vapor concentration of the chamber is monitored throughout the conditioning phase using electronic sensors, gas chromatography, infrared, or other spectroscopic methods. They may be used for product release also.

(c) EO Gas Concentration Measurement

Throughout the exposure time, chamber atmosphere is measured for estimating EO concentration at frequent intervals using analytical methods. Particular attention should be given for the direct measurement of EO concentration during the first and last phase of EO exposure. The reproducibility and accuracy of the results from direct analysis should be determined during validation of the sterilization process. Parametric release of sterilized medical devices is not a preferred indicator of sterility in health-care facilities. For this purpose, the most difficult and challenging representative of routine load should be used to show the ability of the sterilization process to achieve the intended SAL. The representative product load used in the efficacy testing should typically present challenging load size, configuration, characteristics of packaging material, and lethality conditions such as penetration of heat, humidity, and EO gas diffusion. Medical devices subjected to re-sterilization shall be aerated between exposures to ensure the EO residues in the product do not affect the safety of the workers and the next microbiological run. Precautions should be taken to maintain the normal ambient conditions representative of a routine sterilization process.

In addition to the routine control and monitoring, rigorous microbiological and physical testing should be performed to demonstrate the efficacy and reproducibility of the sterilization process.

(a) *Microbiological Testing*

Microbiological testing shall be performed using defined process parameters such as temperature, humidity, and/or EO concentrations run at lower set points than normal sterilization specifications to deliver less lethality than the routine sterilization process. Exposure time is the key parameter varied during microbiological testing to confirm the effectiveness of the specified sterilization process. The lethality of this designed test cycle shall be determined by either BI/bioburden approach or overkill approach for the procurement of SAL.

Data from lethality studies are used to establish the minimum EO gas exposure time required for efficient sterilization. Lethality is primarily influenced by exposure time, EO concentration, humidity, and temperature. Regardless of the microbiological challenge method used, it is assumed that homogeneous population of microorganism and constant process parameters are maintained from run to run.

(b) *Physical Testing*

Physical testing shall be performed by running a minimum of three planned sterilization processes with all specified criteria of a routine sterilization process. The physical testing shall confirm the attainment of minimum temperature and humidity of product at different phases of the sterilization process, pressure rise and the quantity of EO used, or the concentration of EO in the sterilizer chamber. If these process parameters are not maintained within the defined limits throughout the sterilization process, a detailed investigation on performance, determined process parameter set points, and sensor functioning should be conducted. Upon modifications additional runs might be necessary. Failure among any of these planned runs to demonstrate

the product sterility or functionality during and/or after sterilization process requires further corrective measures and if needed rejection of the sterilized product.

The accuracy and reliability of the equipment to control and monitor sterilization process for achieving the required SAL should be monitored periodically. The equipment should be maintained and/or calibrated on a routine basis in accordance with manufacturer's recommendations, as well as national, regional, or local requirements. Failure to calibrate or maintain the sterilization equipment shall generate inaccurate readings of the process parameters during sterilization cycle.

5 Sterility: Post-sterilization Processes

Following a sterilization process, number of functionality tests ranging from a simple visual inspection to a battery of specialized microbiological or analytical tests may be used to demonstrate that the sterilization process adopted does not affect the functionality of the sterilized medical device and its packaging system. For further details on microbiological tests of sterility, refer 11737-2. Evidences on the assessment of product bioburden or its relative resistance to internal PCD should be validated. The biological safety of the sterilized medical device and/or its packaging system by controlling the EO residual levels should comply with ISO 10993-7.

The criteria for confirming the sterility of the medical device and/or its packaging system following sterilization require that all process parameter specifications (parametric release method) are met during sterilization process; and there is no growth of test organism from any BI. If any one or more of the conformance criteria mentioned above are not fulfilled, then the product shall be considered as nonconforming and will be handled in compliance with ISO 13485. The cause of failure of the sterilization process should be investigated, and the decision on product release should be performed by qualified individuals.

In the event of failure to meet the physical specifications due to a failed controlling or monitoring sensor, the run should be rejected, unless there is an assignable cause and the data from the remaining sensors are within specification. In the event of observations of growth from BI, it is not recommended to release the product based on the acceptable/positive results of the product test for sterility. If medical device needs to be re-sterilized, special care should be taken to minimize the effects of multiple sterilization processes on the suitability of product and its packaging system, product functionality, EO residual levels, and/or reaction products.

6 Packaging of Sterilized Product

During sterilization, the minimum package used to prevent the ingress of microorganisms withstands the sterilization conditions and remains intact to ensure the aseptic presentation of the sterilized medical device until use, defined as sterile barrier system (SBS). When selecting the materials for packaging system for a medical

device that is to be sterilized, the ability of the product to tolerate chemical and physical changes caused by EO and/or any diluents over the anticipated range of sterilization conditions shall be confirmed. The permeability of the material to ensure EO penetration is of utmost importance. The packaging system should also be able to allow gases to vent into and out of package without damage to or rupture of seal integrity, as air removal is part of EO sterilization. The ability of SBS to protect the sterile condition of medical devices during customary handling, EO sterilization process, and distribution should be validated. Effects of exposure to multiple sterilization processes on packing material properties such as permeability, physical strength and dimensions may also be evaluated. Further considerations for packaging are addressed in detail in ISO 11607-1 and ISO 11607-2.

7 Limitations

EO is a highly penetrative toxic gas, and therefore it is important to ensure patient safety by minimizing residual EO and its by-products such as ethylene chlorohydrin (ECH; when EO reacts with free chloride ions) and ethylene glycol (EG; when EO reacts with water) following sterilization. Exposure limits of EO and ECH have been specified in ISO 10993-7; however, exposure limit for EG has not been set, as the risk assessment indicates biologically significant residues of EG to be unlikely when the EO residues are controlled.

Processing of materials contaminated with causative agents such as spongiform encephalopathies, such as scrapie, bovine spongiform encephalopathy, and Creutzfeldt-Jakob disease, has not been discussed here. Specific requirements and validation of the process for inactivating these causative agents have been explored in some countries. Refer ISO 22442-1, ISO 22442-2, and ISO 22442-3 for further details. Occupational safety requirements for handling EO, types of EO process (refer ISO 14937), quantification of residual EO and/or its reaction products (refer ISO 10993-7), and national or regional regulations on the limits of residual EO levels in or on the sterilized medical device have not been described in detail, as it is beyond the scope of the present chapter.

Bibliography

1. **ANSI/AAMI ST67:2009**, *Sterilization medical devices—Requirements for products labeled 'STERILE.*
2. **EN 556-1**, *Sterilization of medical devices—Requirements for medical devices to be designated*
3. **ISO 10993** (all parts), *Biological evaluation of medical devices*
4. **ISO 10993-7:2008**, *Biological evaluation of medical devices—Part 7: Ethylene oxide sterilization residuals*
5. **ISO 11135:2014**, *Sterilization of health care products—Ethylene oxide—Requirements for the development, validation and routine control of a sterilization process for medical devices*

6. **ISO 11138-2:2017**, *Sterilization of health care products—Biological indicators—Part 2: Biological indicators for ethylene oxide sterilization processes*
7. **ISO 11140-1:2014**, *Sterilization of health care products—Chemical indicators—Part 1: General requirements*
8. **ISO 11607-1**, *Packaging for terminally sterilized medical devices—Part 1: Requirements for materials, sterile barrier systems and packaging systems*
9. **ISO 11607-2**, *Packaging for terminally sterilized medical devices—Part 2: Validation requirements for forming, sealing and assembly processes*
10. **ISO 11737-1:2018**, S*terilization of health care products - Microbiological methods - Part 1: Determination of a population of microorganisms on products*
11. **ISO 11737-2:2009**, *Sterilization of medical devices - Microbiological methods - Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process*
12. **ISO 13485:2016**, *Medical devices—Quality management systems—Requirements for regulatory purposes*
13. **ISO 14161:2009**, *Sterilization of health care products—Biological indicators—Guidance for the selection, use and interpretation of results*

An Overview on Sterilization of Health Care Products using Moist Heat: ISO 17665

Renjith P. Nair and Sunitha Chandran

1 Introduction

Medical devices that come in direct or indirect contact with humans, need to be sterile for clinical use. Medical devices may get exposed to microorganisms during its synthesis or its handling by any personnel during packaging or storage. Even if the medical devices are manufactured according to the standard manufacturing conditions, there will be a chance for the presence of one or more type of microorganism, at least in very few numbers. Hence, sterilization of medical devices becomes very important and mandatory. Sterility of any medical device cannot be guaranteed fully. Probability of survival of microorganisms in a device is determined by its type, number, and resistance towards any particular sterilization technique. Detailed description from all or any of the manufacturer or supplier regarding device material properties, packaging, and sterilizer equipment should be assessed prior to the selection of sterilization method. Also, sterilization of medical device using one particular method may not guarantee complete eradication of all the microbial population from the device, and hence sterility assurance level (SAL) shall be developed for each product type and load configuration. The specifications defining the probable level of microorganisms and requirements for defining sterility of medical devices may vary between countries and need to be validated and implemented accordingly.

R. P. Nair
Division of Thrombosis Research, Department of Applied Biology, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Science and Technology, Thiruvananthapuram, Kerala, India
e-mail: renjith@sctimst.ac.in

S. Chandran (✉)
SCTIMST TIMed, Biomedical Technology Wing, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Thiruvananthapuram, Kerala, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_10

Low cost, being environment-friendly, and simplicity make steam sterilization most adapted sterilization method. For steam sterilization, medical devices are exposed to moist heat at specific temperature and pressure inside a sterilization chamber. Penetration of moisture makes microorganisms more vulnerable to die by denaturing its protein content, thereby lowering the time and temperature required normally to kill them. Ensuring attainment of specific temperature for definite time period is crucial for effective steam sterilization, and reproducibility should be validated for each process. ISO 17665 defines the specifications and requirements for the development of a steam sterilization process. The standard also describes the process validation, followed by implementation, quality control for installation, operational and performance assessment. ISO 17665 consists of three parts. This chapter focuses more on ISO 17665-1, discussing the general requirements for the development, validation, and control of a steam sterilization process for medical devices. Part 2 of the standard details the technical specifications for the application of ISO 17665-1, and part 3 provides guidance on the designation of a device to a product family and processing type.

2 Pre-sterilization

For each medical device or product, minimum level of sterility assurance required should be known prior to sterilization. For establishment or attainment of SAL, knowledge of bioburden is also required. Limiting values for temperature, pressure, dwell time, etc. for each material, load size, and its combination shall be tested before the steam treatment. If the product requires any pre-treatment, it may be specified along with product details while supplying the medical device. For packed devices, effective penetration or contact with the steam throughout the device surface should be ensured. As per ISO 17655, the personnel assigned to carry out responsibilities or processes should be having proper training and qualification. Responsibilities and authority of the personal should be well defined and documented under the quality management systems.

3 Steam Sterilization Process Specifications

To ensure the efficacy of sterilization, descriptions of process, equipment used, and product to be sterilized are required. Availability of specifications as detailed in ISO 17655 aids in choosing the optimum sterilization process for each device type based on the raw material, type, maximum withstanding ability, etc. Repeatability of the sterilization protocol is ensured when any international or national standards are followed.

4 Sterilizing Agent

Steam when comes in contact with the microbes, translates thermal energy to the microorganisms and kill them. Moist heat may be introduced as saturated steam or by applying heat into the chamber such that the water content already present in the device generates steam. Saturated steam is preferred over superheated steam due to its microbial effectiveness. Sterilization load, initial temperature, and product type determine the energy requirement for each sterilization type. The heat transfer medium used should be free from pyrogen and exhibit uniform flow within sterilization chamber. The amount of water suspended in saturated steam entering the chamber should be minimum, such that the water content should not affect the product integrity and packaging.

Different steam sterilization processes include saturated steam venting, saturated steam with active air removal, steam mixtures, water spray, and water immersion. Saturated steam vented process is used for surface contact sterilization. The process includes a heating phase, wherein sterilizer chamber is filled with saturated steam until the specific temperature or pressure is attained followed by plateau phase during which physical parameters are maintained for particular time and finally during cooling phase, where air or solution is vented into the chamber until the chamber pressure normalizes to atmospheric pressure or attains a safe temperature. When saturated steam processes are used, steam penetration test needs to be done, which confirms that level of non-condensable gas in the sterilizer chamber does not prevent saturated steam from reaching the device surface. Devices with pores, lumens, or cavities, or certain packed devices have to forcefully remove air prior to and after steam exposure. In such processes details of the product and container, support system within the chamber, temperature profiles to attain lethality, etc. need to be mentioned.

5 Equipment Specifications

Specifications of equipment used for sterilization need to include the type of material used; design, location, and characteristics of sensors used within or outside. Material type used for making the equipment should resist any chance of corrosion due to moist heat. ISO standard recommends that material coating with amines like hydrazine should be avoided. Guidance on installation of the equipment shall include isolation and details of physical parameters like pressure, temperature, flow, filtration, voltage, and permissible non-condensable gas level. It has to be ensured that the equipment will deliver specific exposure conditions throughout the sterilization cycle, without degrading the product. Adequate reference points may be chosen to ensure effectiveness by using sensors and regular monitoring. Reproducibility of the process specification should be verified at specific intervals. EN 285 specifies guidelines for implementation, validation, and preventive measures to be followed

while using large sterilizers that have a capacity of more than 60 litre or include one or more sterilizer chamber.

6 Sterilization Process

Microbicidal effectiveness of steam sterilization depends on the temperature and duration of the sterilization process. Process specifications need to include step by step operating conditions and parameters to be maintained or attained during the sterilization cycle so as to achieve SAL. Sterilization load mass and size should be defined along with the process specifications. The maximum and minimum limit of these operating parameters also need to be defined for establishing lethality without affecting product performance. As per ISO 17665-2, the most accepted sterilization process parameters are 121 °C for 15 min, 126 °C for 10 min, and 134 °C for 3 min. Usage of temperature higher than the acceptable value creates superheated steam within the chamber which may affect the medical device properties and function. In such cases microbicidal effectiveness needs to be validated and documented prior to implementation of each process. New process specifications need to be tested in a prototype system prior to implementation in the final equipment.

The process should also include strategies by which any error or inadequacy of the equipment to attain any of the process parameters is identified and steps to be followed if any error is found. This will ensure maximum reproducibility of the process type for a particular product family and loading configuration. Process detail also need to include the means to ensure personal and environmental safety.

If an existing process specification for a medical device needs to be applied for a new product family, the challenge identified for the latter should be less than or equal to the loading conditions of existing medical device. Combination of physical parameters like pressure, temperature changes, and duration of exposure also should be validated. ISO 17665-3 may be referred for more details on classification of product family for a specific steam sterilization process.

7 Product Specifications

Product specifications describe material property, tolerance level to specific parameters, packaging (if any), etc. Medical device design and properties influence penetration of steam and sterilization efficacy. Steam sterilization may also affect the device properties or functioning. Hence material data or product information provided by manufactures should be carefully studied before validating the sterilization process. ISO 17665-2 describes more detailed specifications like physical, mechanical, and functional properties.

8 Validation

Validation ensures that the specifications required for each stage of sterilization are met, so as to meet SAL. Any change in the specifications in equipment, process, or product needs to be validated and noted. It includes installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). Installation qualification should validate that equipment installed attains/exhibits maximum and minimum pressure, temperature and allows adequate non-condensable gas flow and water in saturated steam. OQ helps in validating the installed equipment to function and deliver all the specifications required for different steam sterilization processes without any leakage of steam or air. PQ demonstrates that the product has undergone all the sterilization process and was exposed to the process variables to obtain the required sterility assurance level. Measuring holding time, temperature profiling, usage of chemical or biological indicators, or performing test for heat penetration and/or sterility helps in validating PQ. To ensure compliance and repeatability, PQ of three consecutive sterilization processes may be considered.

If temperature profiles for the product sterilizer chamber follow the same as that of a reference material, sterilized product may be released. But for packed devices, the release is made on the basis of integrity of package and the process indicators on the package. There should also be clear indication to identify processed and non-processed items, so as to confirm sterilization process and release the product. Any change in process parameter, device package or packaging procedure, or load configuration or any replacement of equipment part that may change the process parameter may affect the process effectiveness, and such changes need to be documented, and process needs to be revalidated.

9 Sterilization of Packed Devices

Packed medical devices need to be sterilized with care, as the packaging material should not prevent the penetration of steam into the device or interfere with the sterilization process. Pre-existence of moisture within the product or packaging, may interfere with the sterilization process and affect the vacuum application phase. In such cases, steam penetration test needs to be carried out specifically in less accessible areas like lumen, tubing, etc. Along with the penetration efficacy, the packing material or design should be able to cope up with all the changing parameters of temperature, pressure, etc. that the device would be subjected to during the process of sterilization.

10 Indicators for Assuring the Efficacy of Sterilization

Indicators are needed to make sure that proper and complete sterilization of the medical device has been achieved. It can be biological or chemical indicators. Biological indicators used during moist heat sterilization process should comply with ISO 11138-3 (the standard that specifies the requirements for inoculated carriers, test organisms, etc., determination of its resistance, carrier packaging, and testing methods employed). If chemical indicators are used, it should comply with ISO 11140. The chemical indicators used shall not react with or contaminate the device at any phase of sterilization and affect device properties or function. Use of indicators also requires that their location and acceptance range need to be clearly defined.

11 Assessment of Effectiveness

In certain cases, to ensure the efficacy of sterilization, devices should be preconditioned; if so, it should be clearly mentioned in the sterilization protocol. Postconditioning, medical devices shall be cleaned and disinfected properly prior to sterilization. Complete removal of moisture from the device surface may be confirmed prior to packing of the sterilized material. It should also be ensured that steam sterilization didn't affect the device composition or conformation, thereby affecting its indented use or application. Contaminants get retained in some rare cases even after sterilization, and the limiting value for maximum level of contaminant should be identified for each device.

For assessing effective sterilization, biological or chemical indicators are used as discussed earlier. Chemical indicators should be tested for the effect of minimum and maximum temperatures during the sterilization process. It should be specially mentioned, if post-sterilization medical devices need to be treated separately to maintain the sterility. ISO standard also recommends having a system to distinguish processed and the non-processed medical devices. Processed devices should meet all the criteria to confirm that processing has been done as per the established process and equipment requirements for steam sterilization. Quality assessments should be routinely done for assessing the efficacy of the process, equipment, and processed device.

12 Sterilization of Used Medical Devices

Used medical devices may carry a wide variety of microbes and other contaminants. Hence it should be made sure that the used medical devices along with its packaging are thoroughly cleaned and disinfected prior to the sterilization process. Re-sterilization of medical devices may need additional validation requirements as

earlier steam sterilization might have increased material thickness and crack could have formed in some devices. When such devices are to be sterilized, longevity of the material should be known prior to re-sterilization. Guidelines for the specifications for treating re-sterilized medical devices are detailed in ISO 17664 and EN 868-8.

13 Limitations of Steam Sterilization

Steam sterilization cannot be applied to all materials like polymers and metallic devices due to compatibility issues. It can cause corrosion of some metallic devices, in particular high carbon steel used for surgical and dental instruments, and cause unprotected cutting edges to dull. Moisture also can adversely affect electronics in the device.

Guidelines and protocols have to be developed and validated for the eradication of pathogens causing diseases like encephalopathy and Creutzfeldt-Jakob disease, as ISO 17665 does not cover those. Usage of combination agents with biological agents like steam and formaldehyde is also not specified in the standard. ISO 17665 also does not specify requirements to designate medical devices as sterile and sterilization facility as occupationally safe.

14 Other Standards and Guidelines

Other standards or guidelines related to steam sterilization are EN 285 (specification regarding large steam sterilizers – volume of at least 60 L), ISO 25424 (specifications while using low-temperature steam and formaldehyde), EN 868-8 (specifications for reusable containers for steam sterilizers), EN 13060 (specification regarding small steam sterilizers), ISO 11138-3 (specification for biological indicators), ISO 11140-4 (specifications for chemical indicator used in Bowie-Dick-type steam penetration test), ISO 11140-3 (specifications for chemical indicator used as an alternative to Bowie-Dick-type steam penetration test), ISO 11140-5 (specifications for chemical indicator used in Bowie-Dick-type air removal test), AS/NZS 4187 (comprehensive guidance for sterilization of reusable devices in Australia and New Zealand), CDC/HICPAC (guidance on sterilization of patient care devices in the United States of America), and HTM01-01 Part C (guidance for designing steam sterilizers and its testing in the United Kingdom).

Bibliography

1. ISO 11138-3, Sterilization of health care products — Biological indicators — Part 3: Biological indicators for moist heat sterilization processes
2. ISO 11140-1, Sterilization of health care products — Chemical indicators — Part 1: General requirements
3. ISO 17664, Sterilization of medical devices — Information to be provided by the manufacturer for the processing of resterilizable medical devices
4. EN 285, Sterilization — Steam sterilizers — Large sterilizers
5. EN 868-8:1999 -Packaging materials and systems for medical devices which are to be sterilized —Part 8: Re-usable sterilization containers for steam sterilizers conforming to EN 285 — Requirements and test methods
6. EN 13060, Small steam sterilizers
7. PFLUG, I.J. and KRISTEN, D.E. Carrying out Biological Qualification, the Control Operation of Moist-Heat (Steam Sterilization) Processes for Producing Sterile Pharmaceuticals and Medical Devices PDA, *Journal of Pharmaceutical Science and Technology*, 54 (2) 2000
8. ISO/TS 17665-3 sterilization of health care products — Moist heat —Part 3: Guidance on the designation of a medical device to a product family and processing category for steam sterilization
9. A Practical Guide to Decontamination in Healthcare, Gerald E. McDonnell and Denise Sheard, John Wiley & Sons, 2012, 460 pages
10. Review of surface steam sterilization for validation purposes, Joost van Doornmalen, Ira and Klaas Kopinga, American Journal of Infection Control, March 2008, Volume 36, Issue 2, Pages 86–92
11. ISO 17665-1:2006(en), Sterilization of health care products — Moist heat — Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
12. ISO/TS 17665-2:2009, Sterilization of health care products — Moist heat — Part 2: Guidance on the application of ISO 17665-1
13. ISO 25424:2018, Sterilization of health care products — Low temperature steam and formaldehyde — Requirements for development, validation and routine control of a sterilization process for medical devices
14. ISO 11140-3:2007, Sterilization of health care products — Chemical indicators — Part 3: Class 2 indicator systems for use in the Bowie and Dick-type steam penetration test
15. ISO 11140-4:2007, Sterilization of health care products — Chemical indicators — Part 4: Class 2 indicators as an alternative to the Bowie and Dick-type test for detection of steam penetration
16. ISO 11140-5:2007, Sterilization of health care products — Chemical indicators — Part 5: Class 2 indicators for Bowie and Dick-type air removal tests
17. AS / NZS 4187:2014, Reprocessing of Reusable Medical Devices in Health Service Organisations
18. Health Technical Memorandum 01-01: Management and decontamination of surgical instruments (medical devices) used in acute care Part C: Steam sterilization

ISO 10993: Biological Evaluation of Medical Devices

Pugazhenthan Thangaraju and Shoban Babu Varthya

1 Selection and Qualification of Reference Materials for Biological Tests (ISO 10993-8)

Before selection of certified/reference material, a reference material must be available not less than 5 years from the supplier, and it should publish its source and method of processing. Certification of reference material is done by interlaboratory studies. Reference material must be used for screening of biocompatibility of medical devices and prevention of misuse of certified reference material.

2 Chemical Characterization of Material (ISO 10993-18)

Chemical characterization of material is essential for assessing biological safety of the device, quantification of material leached due to clinical use, supporting equivalence with existing device/prototype device and suitability of new device for clinical application. Chemical characterization along with risk assessment increases the biocompatibility of device for clinical use. It also plays an important role in the device's biological evaluation and toxicological risk assessment.

General Principles of Characterization For chemical characterization of device, its composition and quantification of extraction material are essential. Chemical

P. Thangaraju (✉)
Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Raipur, Chhattisgarh, India

S. B. Varthya
Department of Pharmacology, All India Institute of Medical Sciences (AIIMS), Jodhpur, Rajasthan, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_11

composition enables to compare with pre-existing/standard device and also toxicological risk assessment. The extent of chemical characterization is determined by nature and duration of the clinical exposure, physical form of the device used clinically and its previous use. Chemical characterization in biological analysis is essential because potential biological risks are arising from the use of medical devices by risk assessment. A medical device must undergo extraction test to see the potential bioavailability of test material or its additive in the process of manufacturing. It depends on the duration of clinical use and physical characteristics (liquid, gels, polymers, metals, ceramics, etc.) of material used.

Characterization Procedure To assess the risk of the material, characterization of material must have information on composition of finished device including its additives; material must be equivalent to clinically established material. To test the equivalence, a test material is compared with already used material with respect to its composition and extractable profile along with duration of contact and invasiveness and leachable material, and it must have better toxicological profile or similar toxicological profile. While establishing composition and configuration of device, the hypothetical worst-case scenario will be taken from source of material or appropriate compositional testing. Quantitate information of material to describe the total amount of chemical present in the material. Quantitative risk assessment is done with existing toxicological information.

Chemical characterization parameters and methods are essential for the stepwise generation of qualitative and chemical quantitative characterization data used in the risk assessment.

1. For material composition based on material type, analytical test varies. In case of synthetic polymers, chromatographic (GC, LC), spectrophotometric and fluorescence techniques are used. In case of metals and alloys, X-ray fluorescence, electron microscopy, etc. are used. In case of ceramics, X-ray fluorescence, ion chromatography, etc. are indicated.
2. For extractable and leachable compounds: In case of organic compounds based on volatility, headspace sampling for gas chromatography (HS-GC) is typically used to analyse VOCs, gas chromatography (GC) is typically used to analyse SVOCs, and LC is used to analyse NVOCs.
3. For structural composition or configuration, spectrophotometric studies are indicated.

Reporting of analytical tests used chemical characterization done in a format, which includes description on test material and sample preparation, analytical method and extraction conditions, stability testing, analytical evaluation threshold and qualitative and quantitative data, along with clinical exposure to chemical.

Below we will be discussing specific parameters and methods used for characterization of materials:

3 Physicochemical, Morphological and Topographical (PMT) Characterization of Materials (ISO 10993-19)

PMT characterization along with above framework is essential for judging a proposed material to clinical established material or a prototype device to final device. Few examples to understand the relation between PMT evaluation and clinical effectiveness are as follows:

1. Porous materials as surfaces on orthopaedic implants can encourage tissue ingrowth at the surface of the implant for better integration.
2. The use of material scaffolds and meshes aids in healing process.
3. The PMT characterization enables to understand the bacterial adherence to catheters and their role in infections and blockages.
4. Alterations to the microtopography of surfaces, e.g. producing microgrooves or other defined patterns, have been shown to influence the adhesion and direction of movement of certain types of cells on that surface.
5. For certain medical devices, e.g. orthopaedic implants and vascular prostheses, mechanical properties may influence biological responses such as tissue remodelling.

4 Framework for Identification and Quantification of Potential Degradation Products (ISO 10993-9)

Under this we will be looking at general principles for systemic evaluation of the potential and observed biodegradation of medical devices and for the design and performance of biodegradation studies. It depends on nature of material and its anatomical location during use. Study design depends on chemical and physiochemical properties, surface morphology and biochemical properties. In case of biodegradable material or material implanted for more than 30 days or toxic substance released from the material, biodegradable studies shall be conducted. But in case if biodegradable products are similar to parent material or if safety data is available, then there is no need to conduct further studies. When studies are planned to study, then in vitro and in vivo studies are to be conducted.

Characterization of potential degradation products: Degradation products can be particulate or soluble compound or ions; based on type of particulate matter, it must be characterized (if particulate material, then size, shape, surface area and other relevant characteristics recorded). Protocol of such study must aim at evaluating the changes in bulk material and mechanism of change in its characteristics. Bulk material undergoes changes during storage, or processing, or sterilization, during implantation or after implantation, or leeching from the site of implantation. Substance from implant can be released by chemical reaction, leeching, migration, depolymerization or peeling of material.

A study must report nature of material and its intended use, assessment of degradation and its rationale for same, description of degradation products related to test material and methodologies including analytical test and statement of compliance to good laboratory practice.

5 Identification and Quantification of Degradation Products from Polymeric Medical Devices (ISO 10993-13)

Under this we will be discussing tests in a stimulatory environment for identifying and quantification of degraded products from polymeric medical devices.

Test Designs Analytical methods designed to test the polymeric materials are solution viscometry (molecular mass average, branching); swellability (cross-link density); rheology (melting range, melt viscosity, thermal stability, molecular mass distribution); chromatographic methods (e.g. gas and/or high-performance liquid chromatography for residual monomers, additives and leachables; size exclusion/gel permeation chromatography for molecular mass averages and changes in molecular mass distribution; mass spectrometry for identification); spectroscopic methods (e.g. ultraviolet spectroscopy, infrared spectroscopy, nuclear magnetic resonance, mass spectroscopy for identity, composition, distributions; atomic absorption spectroscopy for catalyst content, heavy metals); and thermal analysis (e.g. differential scanning calorimetry for glass transition, melting range or softening point, blends).

Test solution must mimic the biological state in which it is intended for use. For example, for hydrolytic degradation, grade 2 laboratory water is used along with buffer. Similarly for oxidative degradation, water and hydrogen peroxide with Fenton's reagent will be used.

5.1 The Accelerated Degradation Test

This is a screening method to identify and/or quantify degradation products. This test is conducted between 37 °C and less than melting point of polymer. Duration of test depends on intended clinical use of the material. (For devices whose intended use is longer than 30 d, test periods of 2 d and 60 d shall be used. For devices whose intended use is less than 30 d, test periods of 2 d and 7 d shall be used.)

5.2 Real-Time Degradation Test in a Simulated Environment

Carry out the test at 37 ± 1 °C.

Test Period For devices whose intended use is longer than 30 d, test periods of 1 month, 3 months, 6 months and 12 months shall be used. For devices whose intended use is less than 30 d, four alternative test periods shall be used, including 30 d.

5.3 Test Report

Description of the test material, batch or lot number, dimensions and number of samples tested; test solution and conditions; detailed description and justification of the test methods used, including (where appropriate) specificity, sensitivity, detection and quantification limits; method used to determine mass loss, including precision; mass/volume ratio of sample and shape of sample; sample pretreatment and drying method; selected pH; test temperature; test periods; test results; (1) mass balance; (2) molecular mass/distribution (cross-link density); (3) results of tests run on the solution, debris and/or bulk polymer; (4) identified degradation products; (5) rationale for final decision.

6 Identification and Quantification of Degradation Products from Ceramics (ISO 10993-14)

There are two tests available.

An Extreme Solution Test This is conducted at low pH, based on a low pH citric acid buffer solution. This test can be used for screening of all ceramics. Best results are obtained if specimen run on granulated specimen. Characterization of test sample shall be done by gas absorption, density, solubility, microstructural and X-ray diffraction method.

Simulation Solution Test This test is performed at physiological pH (7.4 ± 0.1). This test is applicable to all ceramics to see that degradation products are generated under simulated test conditions. Test specimens shall be prepared as coatings on blank discs for getting finished products. Surface area, microstructure and X-ray characterization shall be recorded after the procedure.

7 Identification and Quantification of Degradation Products from Metals and Alloys (ISO 10993-15)

A potentiodynamic test and a potentiostatic test are used to identify and quantify degradation from metals and alloys.

8 Compatibility Testing

8.1 Biocompatibility (ISO 10993)

8.2 Selections of Tests for Interactions with Blood (ISO 10993-4)

In this section, we will discuss on devices coming into contact with blood. They may be externally communicating devices like cannulae, IV catheters, cardiopulmonary bypass circuit, capillary filters, guiding wires, etc. and implant devices like AV shunts, IVC filters, ventricular assist devices, vascular stents, etc.

Characterization of Blood Interaction For characterization of devices, they need to undergo certain test for interaction like haemolysis due to device or mechanical force and thrombosis.

In Vitro Tests Haematocrit, anticoagulant (type and amount), test sample preparation, test sample age, blood/blood component age, test sample storage, aeration and pH, temperature, proper randomization, test sample surface area to blood volume ratio and, for dynamic studies, fluid flow conditions, especially flow rate, wall shear rate and pressure(s).

Ex Vivo Tests Platelet adhesion, emboli generation, fibrinogen deposition, thrombus mass, white cell adhesion, platelet consumption and platelet activation.

In vivo testing involves implanting the material or device in animals. This primarily tests the patency of a conduit or device. The percent of occlusion and thrombus mass are determined after the device is removed. The tendency of thrombi formed on a device to embolize to distal organs should be assessed by careful gross as well as microscopic examination of organs downstream from the device. In addition, histopathological evaluation of the surrounding tissue and organs is useful (e.g. in case of ventricular assist devices or artificial hearts, the kidney primarily gets affected by emboli).

Arteriograms or imaging from intravascular ultrasound (IVUS) catheters are used to determine patency or thrombus deposition on devices. Radioimaging can be used to monitor platelet deposition at various time periods in vivo; platelet survival and consumption can be used as indicators of blood/device interactions and passivation due to neointima formation or protein adsorption.

In vivo test protocols should contain precise and stand-alone sections stating how each test category identified for testing, i.e. haemolysis, thrombosis, coagulation, platelets, haematology and complement system, will be evaluated.

Preclinical Evaluation of Cardiovascular Devices and Prostheses

Animal studies are conducted to study interactions or potential interactions, which are to be prevented to make device suitable. These are adsorption of plasma proteins, lipids, calcium or other substances from the blood onto the surface or into the device; adhesion of platelets, leukocytes or erythrocytes; formation of pseudointima or neointima on the blood contacting surface and tissue capsule on the surface of the device; alterations in mechanical and other properties of the device; activation of platelets, leukocytes or other cells, or activation of the coagulation, fibrinolytic or complement pathways; formation of thrombus on the device surface; embolization of thrombotic or other material from the device's surface to another site within the circulation; injury to circulating blood cells resulting in anaemia, haemolysis, leucopoenia, thrombocytopenia or altered function of blood cells; injury to cells and tissues adjacent to the device; intimal hyperplasia or accumulation of other tissue on or adjacent to the device, resulting in reduced flow or affecting other functions of the device; and adhesion and growth of bacteria or other infectious agents on or near the device.

Advantages and Limitations of Animal Models

They help for simulation of test device and continuous monitoring for device, but its usage was restricted by size of the animal, duration of implantation and cost.

Advantages and Limitations of In Vitro Models

Avoidance of costly animal models; high replication testing of test objects alongside controls and reference materials using the same batch of blood and, at the same time, use of human or animal blood where flow, temperature and anticoagulation are standardized; worst-case scenario testing, where activation products accumulate without clearance by kidneys or liver or other organs and activation-inhibiting functions of endothelial cells are absent; and isolation from confounding factors associated with device implantation/tissue injury associated with in vivo usage.

Recommended Laboratory Tests

Thrombosis This is analysed from the distal organ microscopy after autopsy. In this we look for per cent of occlusion, surface area covered by thrombus and surface area free from thrombus.

In Vitro Haemocompatibility Haemolysis can be screened by testing plasma haemoglobin levels; the higher the value, the higher will be the haemolysis. Coagulation: Thrombin-antithrombin and fibrin assay using ELISA method indicates reflective of

the level of coagulation activity. Partial thromboplastin time (PTT) is to test the activation of intrinsic coagulation pathway. The activated partial thromboplastin time (APTT) must be avoided because the activator used in this test may interfere with material activation.

Methods to Test the Activity of Platelets Medical devices can cause platelet depletion due to adhesion, aggregation and/or sequestration. To assess the activity of platelets, platelet granule-release proteins beta-thromboglobulin (ß-TG) and platelet factor 4 (PF4), thromboxane B2 (TxB2) and platelet morphological changes are to be tested.

Methods to Test Haematological Parameters Complete blood count, including peripheral smear, leukocyte activation by estimation of leukocyte on the surface of the device or their presence on the thrombi along with platelets.

Estimation Complement Cascade Parameters C3a and SC5b-9 using ELISA. Complement system plays an important role in innate immunity of the body.

8.3 Tests for In Vitro Cytotoxicity (ISO 10993-5)

Three categories of test are used for in vitro cytotoxicity studies: extract test, direct contact test and indirect contact test. These are primarily to study the biological response of mammalian cells to medical devices and/or their extracts.

Endpoints under this test are (1) assessments of cell damage by morphological means, (2) measurements of cell damage, (3) measurements of cell growth and (4) measurements of specific aspects of cellular metabolism.

Tests Used Under In Vitro Cytotoxicity

1. **The extract test**: In this test we simulate or exaggerate the condition intended for use to assess the potential toxic effects in sample by fusion, melting or any alteration of the chemical structure, unless this is expected during clinical application. In case where two or more substances are mixed in sample, then extraction test shall be applied before washing the sample to remove residues. Extraction vehicles in this test can be culture medium with serum, physiological saline solution or other vehicles.
2. **Neutral red uptake (NRU) cytotoxicity test:** In this test BALB/c 3T3 cell lines are used and seeded in 96-well cell plate for 24 h. At different concentrations test sample will be applied for 24 h. The *IC*50 (i.e. the concentration producing 50% reduction of NRU) is calculated from the concentration-response and expressed as a dilution percentage of the extract.

3. **Colony formation cytotoxicity test:** V79 cells are seeded into six-well plates and maintained in culture for 24 h to start growing in a logarithmic phase. They are then exposed to the test compound over a range of concentrations. They are incubated for 6 days to make colonies large enough to count. Colonies are fixed with methanol, stained with Giemsa solution and counted. If the extract exhibits a cytotoxic effect on the cells, the *IC*50 (the concentration inhibiting plating efficiency to 50%) is calculated and expressed as a percentage of the extract.
4. **MTT cytotoxicity test (direct contact test):** Test protocol is based on the measurement of the viability of cells via metabolic activity. L929 cells are seeded into 96-well plates and maintained in culture for 24 h (≈1 doubling period) to form a semi-confluent monolayer (see Reference [5] for more information on cell maintenance and culture procedures). They are then exposed to the test compound over a range of concentrations. After 24 h exposure, the formazan formation is determined for each treatment concentration and compared to that determined in control cultures. For each treatment the percentage inhibition of growth is calculated.
5. **XTT cytotoxicity test (**indirect contact test**):** This is based on the measurement of the viability of cells via mitochondrial dehydrogenases. L929 cells are seeded into 96-well plates and maintained in culture for 24 h (≈1 doubling period) to form a semi-confluent monolayer (see Reference [5] for more information on cell maintenance and culture procedures). They are then exposed to the test compound over a range of concentrations. After 24 h exposure, the formazan formation is determined for each treatment concentration and compared to that determined in control cultures. For each treatment the percentage inhibition of growth is calculated.

9 Toxicity Screening

9.1 Sample Preparation and Reference Materials

9.2 Evaluation and Testing Within a Risk Management Process (ISO 10993-1:2009)

To prevent the potential risk arising from the medical devices (from now we called it as devices) to humans, their biological evaluation is essential. Biological evaluation is done by in vitro and ex vivo tests using animal to identify potential adverse response.

The primary role of this document is to serve as a framework to plan a biological evaluation. A secondary role is to utilize scientific advances in our understanding of

basic mechanisms, preferably physical, chemical, morphological and topographical characterization testing and in vitro models than the in vivo models.

Biological evaluation is done through extensive literature search to know the existing information on physical and chemical characteristics of device, nonclinical and clinical safety and toxicological data of the device. Details of this will be discussed in their respective frameworks. If there is gap in the literature, risk analysis is performed to complete the data sets needed for the biological evaluation of the particular medical device.

Re-evaluation of test material is necessary, if there is a change in source of material, or change in processing or its transport, or change in its intended use or adverse events are observed in humans after their use.

Biological evaluation is done by weighing between risks and benefits by devices. Any acceptable risk after getting expected benefit from the device is considered to be acceptable. Initially risk assessment is done from the identified and estimated risk of a device in contact with biological material. After risk analysis, risk estimation is done from the use and hazards of device. Finally risk management is done after taking risk control measures and improving overall acceptability of the device.

9.3 Animal Welfare Requirements (ISO 10993-2)

Primary aim of ISO is protection of humans from any adverse events or potential adverse events due to medical devices. In this respect, animal studies are conducted to study the biological effects of medical devices. These tests are conducted in humanly approach. Animal welfare primarily focuses on minimization of animal use, minimizing or eliminating the pain and distress and replacement of animal test, if alternative tests are available. Animal welfare primarily deals with vertebrate non-human species.

In this part we will be discussing what essential prerequisites for testing medical devices in animals are.

Essential Requirement for Minimizing or Eliminating Pain and Distress in Animals Under this all experiments are conducted in accordance with legal provisions of their jurisdiction and ethical provisions. Number of animals in each group must be based on literature search, data sharing and replacement of animals wherever possible and appropriate test strategy and study design. All these experiments are conducted in good laboratory care and presence of competent personnel and expert veterinarian service to alleviate their suffering.

Justification of Animal Studies Animal studies are useful for characterization of medical device, when there was no validated test available. But such method must follow the refinement and reduction of animals in the study. These studies must be relevant to their endpoints; data must be part of characterization of medical device.

Planning and Performance of Studies Species selection, number of animals per group, test used in characterization of device and measures taken to minimize or prevent pain and distress at the discretion of expert but must be in compliance with local ethical committee prerequisites and their legal provisions.

Reuse Reuse of animals is warranted to reduce the cost of animal welfare and minimize number of animals used, but in such condition reuse must be based on scientific objective, because pain and distress in the course of experiment may interfere with other test. Whenever animals are reused, it must be well documented.

Test Strategy Test strategy follows appropriate hierarchical approach to minimize the number of tests and to reduce pain and distress to the animals. Animal test must not be performed if adequate data relevant to such test is available.

Animal Care and Accommodation Animal care and accommodation must be according to the national or international animal care, accommodation and husbandry guidelines. Compliance to such guidelines must be justified and documented. Animals which are social species must be housed in groups except during experiment if required. In case single housing is required, it must be documented for that duration. In case animals require restraint, then such application must be minimum duration and degree of restraint to meet scientific objective. In case of surgical procedures, surgeries are conducted under adequate anaesthesia and prevent chances of sepsis along with proper pre-, intra- and post-operative care of the animals.

Humane Endpoints A competent person must supervise animals at least once in a day, and observation number increased, if number possible adverse welfare outcomes present. If animals are in severe pain and/or distress and cannot be alleviated, such animals must be euthanized immediately. Euthanasia of animal is done by using methods which can cause rapid irreversible loss of consciousness of animal.

Study documentation: Under this all experiments must be documented related to the test strategy, the rationale for use of specific species, strain and numbers along with number of animals per group and procedure followed in the study, health status of animals during study protocol, details of the care and husbandry systems, the observation schedules and humane endpoints to be implemented, the contact details for key personnel, the method of euthanasia and the justification for the choice of method to be used and details of the analytical and statistical methods to be applied.

Validity of Test Results and Mutual Acceptance of Data Mutual acceptance of test data can significantly reduce animal test requirements and facilitate timely and ethical regulatory decisions. Whenever possible, test methods shall be based on internationally recognized protocols and conducted in accordance with recognized quality assurance systems, for example, in accordance with the principles of good laboratory practice.

9.4 Tests for Local Effects After Implantation (ISO 10993-6)

In this part we will be discussing about test methods for assessment of local effects by direct contact samples. This test applies for solid and non-absorbable; non-solid, such as porous materials, liquids, gels, pastes and particulates; and degradable and/or absorbable, which may be solid or non-solid.

9.5 Tests for Systemic Toxicity (ISO 10993-11)

In this part we will be discussing procedures followed in evaluating the potential systemic toxicity associated with medical devices. Generally systemic toxicity studies are conducted based on mode and duration of use. Tests are conducted on final or representative product, and it depends on the physical and chemical properties of device like pH, solubility, osmolality, etc. Dose of the study is determined from in vitro acute toxicity and in vitro cytotoxicity studies. Animals are selected based on type of device and their intended route of use (e.g. for acute oral, intravenous, dermal and inhalation studies of medical devices, the rodent is preferred with the option of the rabbit in the case of dermal and implantation studies. Other non-rodent species may also need to be considered for testing, recognizing that a number of factors might dictate the number or choice of species for study). Preferably single species is used in this study.

Size and number of animals per group: For systemic toxicity studies, it depends on number of animals used per dose level and duration of therapy. In the below table, we will be mentioning minimum number of animals per group required based on treatment duration. Matching control group to match with test sample preparation and treatment procedure.

Recommended minimum group sizes:

Study type	Rodent	Non-rodent
Acute	5	3
Subacute	10 (5 per sex)	6 (3 per sex)
Subchronic	20 (10 per sex)	8 (4 per sex)
Chronic	30 (15 per sex)	

As the duration of therapy is increasing, we use more number of animals taking the possible mortality due to treatment in long-term therapy. Sex-based grouping is required, if device is used in both sexes.

Single-dose group vs multi-dose group: Single-dose group is used in acute toxicity studies to get mean lethal dose or hazard dose, but to draw dose response curve, we need to have multi-dose group.

Route of exposure: The test route of exposure shall be the most clinically relevant to the use of the device, where possible. If an alternative route of exposure is necessary, it shall be justified.

Dosing: Under this test sample is administered either single dose per day or multiple doses in a day depending on the volume of administration, and test sample is administered mostly at physiological temperature of animal.

Clinical observation:

Respiratory system: Dyspnoea (abdominal breathing, gasping), apnoea, cyanosis, tachypnoea and/or discharge through nostrils

Motor activities: Decrease/increase of somnolence, loss of righting, catalepsy, ataxia, unusual locomotion, prostration, tremors and fasciculation

CNS: Convulsion, reflexes (corneal, righting, myotactic, light, startle reflex).

Ophthalmological: Lacrimation, pupil size (miosis and mydriasis), extraocular muscles (exophthalmos, ptosis), lens (opacity), iritis, conjunctivitis, chromodacryorrhea, relaxation of nictitating membrane

Cardiovascular signs: Bradycardia, tachycardia, arrhythmia, vasodilation and vasoconstriction

Gastrointestinal: Soft stool, diarrhoea, emesis, diuresis, rhinorrhoea, etc.

Dermatological signs: Oedema, erythema, etc.

Other systems if required:

Clinical pathology: To analyse the toxic effects of devices, blood test along with other analytical tests is performed. Sample collection is done as per protocol.

Haematology (clotting potential (PT, APTT), haemoglobin concentration, haematocrit, platelet count, red blood cell count, white blood cell count, WBC differential)

Clinical chemistry (LFT, RFT, lipid profile, blood glucose, serum electrolytes, immunoglobulin, etc.)

Urine analysis for appearance, bilirubin, glucose, ketones, occult blood, protein, sediment, specific gravity or osmolality, volume, etc.

Anatomic Pathology *Under this gross morphological changes in the intact body* after euthanasia or death, discharge from all opening, and cranial, thoracic and abdominal cavities. Gross morphology and histopathology of selected organs done after harvesting adequate tissue.

Acute Systemic Toxicity This information gives about clinical effects on acute exposure to device. Dosage regimen is established based on this study and mode of toxic effects seen. Under this study, data regarding adverse clinical signs, body weight change, gross pathological findings and death (if any) shall be recorded.

Repeated exposure systemic toxicity (subacute, subchronic and chronic systemic toxicity):

1. Health hazards likely to arise from a prolonged exposure

2. The mode of toxic action of a substance
3. Detailed information on toxic effects, target organs, reversibility or other effects and may serve as the basis for safety estimation

9.6 Tests for Irritation and Skin Sensitization (ISO 10993-10)

Medical devices or their release chemicals may cause irritation of the skin and mucous membrane or may cause sensitization leading to delayed type of hypersensitivity reaction. To test such reaction, in vitro test, animal studies and human trials are to be conducted. These tests are performed in case of devices intended as an implant and externally communicating device.

Under this we follow stepwise approach:

Characterization of test material: In this part physicochemical characterization of device shall be done. Details are already discussed.

Literature review: Through literature review essential for extracting information on device or structurally similar components about physicochemical properties, irritation and/or sensitization.

In vitro tests: In silico methods gaining popularity to identify potentially important reactions and sensitization.

In vivo animal tests: In this test we will be demonstrating the potential irritation and sensitization using positive controls. To test the sensitization, we use local lymph node assay in mice, the occluded patch test in guinea pigs or the guinea pig maximization test (GPMT).

Non-invasive human tests/clinical trials: If test material is found negative in animal studies, these are taken for further evaluation.

9.7 Principles and Methods for Immunotoxicology Testing of Medical Devices (ISO 10993-20)

9.8 Tests for Genotoxicity, Carcinogenicity and Reproductive Toxicity (ISO 10993-3)

The assessment of mutagenic, carcinogenic and reproductive hazards (potentially irreversible biological effects) is an essential component of the control of these risks. In this part we will be discussing the test methods that are most acceptable and which will assist for achieving maximum test sensitivity.

Carcinogenicity test: test to determine the carcinogenic potential of medical devices, materials and/or extracts using multiple exposures for a major portion of the life span of the test animal

Genotoxicity test: test using mammalian or non-mammalian cells, bacteria, yeasts, fungi or whole animals to determine whether gene mutations, changes in chromosome structure or other DNA or gene changes are caused by the test samples

Reproductive and developmental toxicity test: test to evaluate the potential effects of test samples on reproductive function, embryonic morphology (teratogenicity) and prenatal and early postnatal development

Risk assessment of these tests is done using different tests. Signals for these studies are drawn from their structure, manufacturing process, degradation products or metabolites and/or their structure activity relationship. Other important parameters are route of exposure, patient population, duration of exposure to device, etc.

Apart from above characteristics of device for carcinogenicity studies, other additional information-related device physical characteristics (particle size and shape, pore size, surface continuity, surface condition, device thickness) and results from implantation and genotoxicity studies. In case of reproductive toxicity testing, direct or indirect cumulative contact duration with reproductive tissue or foetal development and energy depositing medical devices.

Tests for genotoxicity studies: These are used to test the genetic mutation screened using gene mutations (point mutations) and chromosomal damage [structural aberrations such as translocations, small or large deletions and insertions and numerical chromosomal aberrations (aneuploidy)].

In vitro tests	In vivo tests
The test battery shall include: 1. Gene mutations in bacteria 2. Cytogenetic evaluation of chromosomal damage with mammalian cells 3. Mouse lymphoma tk assay 4. Mammalian cell micronucleus test for chromosomal damage and aneugenicity	1. Rodent bone marrow cells chromosomal aberrations, micronuclei in bone marrow or peripheral blood erythrocytes 2. Micronucleus test in rodents 3. Metaphase analysis in rodent bone marrow 4. Transgenic mutagenicity tests

Carcinogenicity Tests To test this, in general a single study for chronic toxicity and carcinogenicity studies are conducted in case of where potential risk is associated with device.

Criteria Materials for which the degradation time is greater than 30 days; materials introduced in the body and/or its cavities with a cumulative contact of greater than 30 days.

Test Methods Under this test human safety factor of 100 (100 times to the maximum dose exposed by human). Dose should be physiologically compatible. And all tests are based on OECD guidelines.

Reproductive and Developmental Toxicity Tests Test procedure followed for F1 and F2 generation based on OECD guidelines with few modification with dose, route of application, extraction media and exposure time.

9.9 Toxicokinetic Study Design for Degradation Products and Leachable (ISO 10993-16)

In this framework we will be discussing principles on designing and performing toxicokinetic studies (absorption, distribution, metabolism and excretion) relevant to medical devices. It is essential to understand the fate of medical devices and their degraded or leachable products. Therefore we will understand the safety and mechanism of adverse events associated with products.

Toxicokinetic studies vary from device to device. Physicochemical and surface morphology of products are essential along with leachable products, if any for designing the study protocol. All analytical tests to be standardized detect and characterize degradation products, leachable and metabolites in biological fluids and tissues. Data must be plotted against different time interval to get information on various kinetic parameters (rate of absorption, bioavailability, bioresorption, clearance, *C*max, *t*max, distribution, elimination half-life and volume of distribution).

Test methods: In general study should be conducted on suitable species and sex. Usually non-radiolabelled substances will be used. If, radiolabelled substances are being used than there is a need to target metabolically stable positions like ^{14}C or ^{3}H.

Absorption It depends on route of administration; bioavailability studies are conducted in case of non-parenteral route of administration.

Distribution Generally radiolabelled compounds are used. In this quantitative estimation, determining the levels of radiolabelled compound in dissected tissues will be done, and in qualitative, using whole-body autoradiography (WBA), or semi-quantitative, using graded WBA reference doses.

Metabolism and Excretion In this test metabolic cages are to be used to collect urine and faeces. In case of collecting volatile gases like CO2, in such situation special devices are to be used.

1. Indications for toxicokinetic studies
2. If a device is undergoing bioresorption
3. If an implant is undergoing significant corrosion or biodegradable compounds or leachable substances are likely to be released from the implant

4. Significant quantity of toxic component or active ingredient or nano-objects released from the medical device

If toxicological or toxicokinetic data is available or clinical safety data on medical device or their leachable products available, in such situation there is no need to conduct toxicokinetic studies.

10 Other Frameworks

10.1 Ethylene Oxide Sterilization Residuals (ISO 10993-7)

In this we will be studying devices which are in contact with patients. For medical devices sterilized by ethylene oxide (EO), it is important to ensure the levels of residual EO, ethylene chlorohydrin (ECH) and ethylene glycol (EG) and risks to patients.

Based on duration medical devices are classified into different categories to avoid more than permissible limit of exposure.

Classification of medical devices is delivered to patients and their permissible limit for EO and ECH.

Categories of exposure	Limited exposure	Prolonged exposure	Permanent exposure
Duration	≤24 h	24 h–30 days	>30 days (lifetime)
Permanent contact devices with EO	4 mg	60 mg	2.5 g
Permanent contact with ECH	9 mg	60 mg	10 g
Prolonged exposure devices with EO	4 mg	60 mg	
Prolonged exposure devices with ECH	9 mg	60 mg	

Device category	EO	ECH
Limited (<24 h)	4 mg	9 mg
Prolonged (>24 h < 30 d)	60 mg/30 d	60 mg/30 d
Permanent (>30 d)	2.5 g/lifetime	10 g/lifetime
Tolerable count limit (TCL)	10 μg/cm^2 or negligible irritation	5 μg/cm^2 or negligible irritation
Intraocular lens	0.5 μg/lens/d	4*EO limit suggested
Blood cell separator (apheresis)	10 mg	22 mg
Blood oxygenators	60 mg	22 mg
Cardiopulmonary bypass devices	20 mg	9 mg
Blood purification devices (haemodialysers)	20 mg	9 mg

Device category	EO	ECH
Drapes contacting intact skin	10 μg/cm^2 or negligible irritation	5 μg/cm^2 or negligible irritation

Adopted from ISO 10933 series

Tolerable contact limits for surface contacting devices and implants (mg/sqcm):
Primary aim is to prevent localized irritation. Tolerable contact limit for EO > 10 μg/cm^2 or negligible irritation. For ECH 5 mg/cm2 or negligible irritation. But in special situations their exposure limit further changes (e.g. EO in intraocular lenses shall not exceed 0.5 μg EO per lens per day, or 1.25 μg per lens).

Determination of EO and ECH Residuals

Ethylene oxide: Ethylene oxide is an irritating inflammable gas and mutagenic, fetogenic and teratogenic.

Ethylene Chlorohydrin This is a flammable liquid that is irritating to body surfaces, acutely toxic and readily absorbed through the skin in toxic amounts. It has weak mutagenic potential, has some potential to produce fetotoxic and teratogenic changes and can produce injury to several organ systems in the body including lungs,kidneys, central nervous system and cardiovascular system.

To evaluate their levels, gas chromatographic test can be performed.

Factors Influencing Product Residual

Material Composition Materials that contain a source of free chloride ions exhibit a wide degree of variation in the concentration of ECH formed; therefore a single device composed of two dissimilar materials may require a representative sample of both materials to ensure accurate analysis.

Packaging Packaging material based on their packing density and the density of the shipping container varies the penetration and dissipation of both EO gas and the other possible residues, which may in turn affect ECH residue levels.

Ethylene Oxide Sterilization Cycle Gas concentration, exposure time, temperature, type of cycle (i.e. pure EO or EO mixtures), humidity (including the quality of the water source), re-evacuations and air washes and the product and load density or the configuration of the product load in the sterilizer can modify the residual levels.

Aeration Residual EO in devices may vary as a function of aeration temperature, load density and configuration, air flow, loading pattern, surface area of products being aerated and aeration time. Some materials demonstrate aeration rates which can roughly double (aeration time reduced by one half) for each 10 °C increase in aeration temperature.

Factors such as humidity, temperature and air flow may influence ECH formation depending on EO content in the product after removal from the sterilizer.

Factors such as humidity, temperature and air flow may influence ECH formation depending on EO content in the product after removal from the sterilizer.

Analysts should be aware of seasonal variations in aeration rates when samples are stored under laboratory conditions which differ from the ambient warehouse conditions. Under certain circumstances, which can best be determined by experience, it may be necessary to hold samples prior to analysis under conditions that approximate the lowest temperature at which the product is likely to be stored during aeration.

D.1.6 Sample Retrieval

Caution should be exercised when product samples are routinely removed for analysis from the sterilization load soon after the sterilization process is completed. Caution should also be exercised when the product sample or an extract thereof is shipped to an analysis site remote from the sterilization site. In such cases, the errors associated with attempting to correlate the residue amounts on samples and on the rest of the load should be recognized and an experiment to establish the relationships between these conditions carried out.

D.2 Controlling variables

Given sufficient experimental evidence on residue diffusion kinetics (e.g. the rate of EO gas dissipation from the packaging for the range of given devices), it may be possible to group devices for quality assurance testing based on similarities of materials, manufacturing processes and use. For such a classification system to work, the variables discussed above must be controlled. Lack of control may yield data about residue levels that are applicable only to the samples analysed.

Extraction Conditions for Determination of Residual EO
Below table represents suggested extraction conditions that could facilitate laboratory operations.

Device contact duration		
Permanent contact (>30 d)	Prolonged exposure (24 h to 30 d)	Limited exposure (>24 h)
Extensive extraction	Simulated use	Simulated use

Adopted from ISO 10993 series

Ethylene Oxide Residue Measuring Methods

EO method	Intralaboratory	Interlaboratory
Headspace method	3.7%	21.3%
Acetone method	4.1%	16.3%
DMF method	2.9%	8.3%
Aqueous method	2.7%	17.0%

Adopted from ISO 10993 series

ECH Methods
If devices are classified under more than one category, rigorous testing is performed.

Allowable limits: In general, maximum allowable limit in case of prolonged exposure and permanent contact are mentioned in the table under heading of 10.1.

10.2 Establishment of Allowable Limits for Leachable Substances (ISO 10993-17)

Risks associated with exposure to hazardous leachable substances are managed by identifying the leachable substances, quantifying the associated risks and limiting exposure within tolerable levels. Allowable limits may be based upon health risks that can be systemic or local, immediate or delayed, and range in severity from minor localized adverse effects to life-threatening risks. A method for the determination of allowable limits for substances leachable from medical devices should be predetermined. It is intended for use in deriving standards and estimating appropriate limits where standards do not exist. It describes a systematic process through which identified risks arising from toxicologically hazardous substances present in medical devices can be quantified.

General Principles for Establishing Allowable Limits Evaluating the biological risk associated with the leachable substance from previous data and critical health-related endpoints, identification of tolerable limit based on route of administration and duration of exposure along with tolerable contact limit in case of irritation as an endpoint. Tolerable exposure depends on patient's body mass index and device utilization factor. Feasibility of test also evaluated based on general approach or case-by-case basis.

Establishment of Tolerable Intake (TI) for Specific Leachable Substances From toxicological data, no observed adverse effect level (NOAEL) is to be established.

Part 22

Guidance on Nanomaterials In this we will be discussing materials which contain or generate nanomaterials. Any structure with 1 nm and 100 nm dimensions is considered as nanomaterial. In this size materials potentially interact with subcellular components like DNA. Therefore it is essential to evaluate the materials which are prepared with nanomaterials, or produced during its use.

Biological risk evaluation of nanomaterials depends on type and duration of contact. Initially extract the available information related to the material, and if the available data suggests acceptable risk, then no further testing is required.

Characterization of nanomaterials: Physiochemical characterization of nanomaterials is essential to understand their behaviour in the biological systems. Physiochemical of material includes their composition, external features and its activity surrounding environment. Toxicological testing of nanomaterial is based on its chemical structure, size, distribution, purity, solubility, etc., along with additional properties like crystallinity, redox potential, radical formation potential, etc.

Chemical composition and purity test, X-ray fluorescence, X-ray photoelectron spectroscopy, Auger electron spectroscopy, scanning electron microscopy + XRD or energy-dispersive X-ray spectroscopy (EDS), nuclear magnetic resonance and single-particle, inductively coupled plasma-mass spectrometry (spICP-MS) can be used.

Particle size and particle size distribution are assessed by dynamic light scattering, small-angle X-ray scattering, size exclusion chromatography, analysis of images of scanning electron microscopy (SEM), transmission electron microscopy (TEM) or scanning probe microscopy (SPM), differential mobility analysis, centrifugal liquid sedimentation, nanoparticle tracking analysis, Raman spectroscopy, laser-induced incandescence, confocal laser scanning microscope (CLSM), single-particle ICP-MS, tangential flow filtration for nanomaterial and separation followed by appropriate detection, e.g. ICP-MS.

Biological tests for nanomaterial are done by using representative test material instead of positive and/or negative controls. A representative test material must be homogenous and stable with respect to one or more specified properties. Currently available reference materials are titanium dioxide, colloidal silica, gold and single-walled carbon nanotubes. Reference materials play a very critical role in the risk assessment of nanomaterials.

Sample Preparation for Testing Nanomaterials Sample preparation for nanomaterials is difficult compared to bulk products because of its size and potentially altered physiochemical properties. Nano-objects have larger surface area leading to more reactivity, formation of aggregates, transformation due to hydration or other processes, etc. The surface area of nanomaterials will be higher than the regular devices and it is important to understand the hazard potential. In case of nanomaterials along with the effects of residues, the nanomaterials to be dispersed in a liquid for direct risk assessment has to be tested. Dispersion test is primarily used for polar products. Endotoxin considered to be most common confounding factor with stock solution is therefore properly evaluated for its contamination. Commonly used test

for this test is limulus amoebocyte lysate (LAL) assay. Sterilization is a mandatory process before preclinical evaluation of nanomaterials.

Release of Nanomaterials from Medical Devices It is necessary to understand the rate of release of particle, its quantity, movement and accumulation in the different parts of the body. This is to be evaluated in special conditions like joint replacement implant because they have potential to bind to cells and their components and cause their anomaly.

Toxicokinetic of Nanomaterials A toxicokinetic study is only required if the nanomaterial has the potential to be released from a medical device and become absorbed, distributed, metabolized and/or excreted. Factors such as route of administration, size of the nano-object or its aggregates/agglomerates, surface properties (chemistry and charge), animal species, dose and dosing methods have all been reported to influence the toxicokinetics in animal models. Toxicological evaluation is done.

In vitro cytotoxicity testing	In vivo testing
In this test, the impairment of cellular functions like the disruption of plasma membrane integrity, interference with organelle function, disruption of the cytoskeleton, etc. tested 1. Neutral red uptake 2. Colony formation 3. MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide] 4. XTT {2,3-bis[2-methoxy-4-nitro-5-sulfophenyl]-5-[(phenylamino)carbonyl]-2H-tetrazolium hydroxide} For the genotoxicity testing: The mouse lymphoma *tk* assay Hypoxanthine-guanine phosphoribosyltransferase (HPRT) mutation assay Double-strand breaks are neutral comet Single-strand breaks are alkaline comet and oxidative damage	In this part apart from toxicokinetic studies, reproductive toxicity, genotoxicity and carcinogenicity studies Commonly performed tests for genotoxicity studies are: Micronucleus test in rodent erythrocytes or bone marrow Chromosomal analysis in rodent bone marrow DNA strand break analysis (in vivo comet assay) Single-cell gel assay Transgenic animal models Commonly performed tests for carcinogenicity studies are: life time bioassays; apart from studies explained earlier transgenic animals like the murine rasH2 model

Immunotoxicity, Irritation and Sensitization In general, immunotoxicity is evaluated during repeat dose toxicity testing (e.g. 28 d or 90 d) during which the first indications for immunosuppression and/or immunostimulation can be detected. In vitro models provide a reliable and preferred method of studying the immune cell function. The impact of nanomaterials on immune cell function can be studied by evaluating signaling pathways, such as the nuclear factor kappa B pathway, in specific immune cell lines. These are phagocytosis, chemotaxis and nitric oxide production by macrophages in addition to many other endpoints.

Nano-objects have been used as haptens or hapten carriers, which indicates that they are capable of exerting an adjuvant activity affecting the immune system. For silver nanoparticles, the effects on the immune system were found to be the most sensitive parameter of systemic toxicity after intravenous administration for 28 d.

Sensitization To assess local toxicity, various tests, such as the Buehler test (BT), guinea pig maximization test (GPMT), local lymph node assay (LLNA), human patch test (HPT) and a modified GPMT (GPMT with surface application), are used. In vivo tests like the direct peptide reactivity assay (DPRA), the human cell line activation test (h-CLAT), etc. are used.

Irritation Irritation tests (including intracutaneous reactivity) should be considered to estimate the irritation potential of medical devices, materials and/or their extracts, using an appropriate site for application such as the skin, eye and mucous membrane in a suitable model. The test(s) performed should be appropriate for the route (skin, eye, mucosa) and duration of exposure or contact. Various properties of nano-objects can affect their uptake after skin, eye or mucosa exposure; these properties include (but are not limited to) size, shape, surface area, surface charge, surface energy/activity, solubility, aggregation state, polydispersity and ion dissolution kinetics. Chemical composition of the main nanomaterial can also affect potential irritation caused by nanomaterials.

Ocular Irritation Test The Bovine Corneal Opacity and Permeability (BCOP) test method and the Isolated Chicken Eye (ICE) test method.

Oral Mucosa Irritation Test After applying test agents in the oral cavity, gross and histological examination done and results are evaluated based on severity of local inflammation from changes.

Penile Irritation Test For acute exposure, note the appearance of the penis in 1 h after the initial application (e.g. immediately prior to the next application) and subsequent treatments. Also observe at 1, 24 and 48 h of post-application.

For prolonged repeated exposure tests, note the appearance of the penis at first hour after the initial application and immediately prior to the next application. Grade the skin surface reactions for erythema accordingly.

Rectal Irritation Test It is indicated in case the material contacts with the rectal tissue during clinical use. In case a test material showed to be skin/eye irritant, those with a pH < 2.0 or > 11.5, then it is characterized as rectal irritant; in such scenario it is not essential to perform rectal irritation tests. A short catheter or cannula is inserted in the rectum and test solution delivered and observed for changes. This test should be repeated for 5 days. Observe for appearance of the perineum for signs of discharge, erythema and irritation. Results are evaluated by macro- and microscopic appearance of rectal tissue by pathologist.

Vaginal irritation test: It is indicated in case the material contacts with the vaginal tissue during clinical use. In case a test material showed to be skin/eye irritant, those with a pH < 2.0 or > 11.5, then it is characterized as rectal irritant; in such scenario it is not essential to perform rectal irritation tests. Healthy young adult female albino rabbits (n = 3) from a single strain weighing not less than 2 kg shall be used. A short catheter or cannula is inserted in the vagina and test solution delivered and observed for changes. This test should be repeated for 5 days. Observe for appearance of the perineum for signs of discharge, erythema and irritation. Results are evaluated by macro- and microscopic appearance of rectal tissue by pathologist.

Human Skin Irritation Test At least 30 volunteers shall complete the test, with no less than one-third of either sex. Apply the test material to intact skin at a suitable site, e.g. the upper outer arm, by means of an occlusive chamber containing a gauze pad. The application site shall be the same in all volunteers and shall be recorded. Generally, the patch shall measure at least 1.8 cm, preferably 2.5 cm in diameter. The patch shall be held in contact with the skin by means of a suitable non-irritating dressing, including non-irritating tape, for the duration of the exposure period. Duration of exposure starts from 15 or 30 min to up to 4 h.

Clinical evaluation is done using observable changes on skin like erythema, dryness and oedema.

In Vitro Tests for Skin Irritation Human skin models can be obtained commercially (e.g. EpiDerm, EPISKIN, Vitrolife-Skin, TESTSKIN, LabCyte EPI-MODEL) or be developed or constructed in the testing laboratory. The preferred ones are EpiDerm and EPISKIN tests.

Haemocompatibility These tests are performed in case of nanomaterials contacting with blood or blood products (biological evaluation materials already explained).

References

ISO 10993-1:2018 Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
ISO 10993-2:2006 Biological evaluation of medical devices Part 2: Animal welfare requirements
ISO 10993-3:2014 Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
ISO 10993-4:2017 Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
ISO 10993-5:2009 Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
ISO 10993-6:2016 Biological evaluation of medical devices Part 6: Tests for local effects after implantation
ISO 10993-7:2008 Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
ISO 10993-8:2001 Biological evaluation of medical devices Part 8: Selection of reference materials (withdrawn)

ISO 10993-9:2010 Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
ISO 10993-10:2013 Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
ISO 10993-11:2018 Biological evaluation of medical devices Part 11: Tests for systemic toxicity
ISO 10993-12:2012 Biological evaluation of medical devices Part 12: Sample preparation and reference materials (available in English only)
ISO 10993-13:2010 Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices
ISO 10993-14:2009 Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
ISO 10993-15:2009 Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
ISO 10993-16:2018 Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
ISO 10993-17:2009 Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
ISO 10993-18:2020 Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process
ISO/TS 10993-19:2006 Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
ISO/TS 10993-20:2006 Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices
ISO/TR 10993-22:2017 Biological evaluation of medical devices Part 22: Guidance on nanomaterials

FDA-CFR Title 21-Food and Drugs: Parts 800 to 1299

Indumathy Jagadeeswaran, Nandhini Palani, and Ganesh Lakshmanan

1 Introduction

(a) *FDA and FD&C Act*

Federal Food, Drug, and Cosmetic Act (FD&C Act) is the legal authority of FDA that regulates the medical devices along with electronic radiation-emitting products. FDA's level of control over these products was provided in the FD&C Act where the act is comprised of regulatory requirements and provisions for FDA to control the products. FDA develops, publishes, and implements regulations and provisions of FD&C Act over medical devices and radiation-emitting products [1].

(b) *Federal Register (FR)*

The FR is an official standard register of FDA, where official daily publication for rules, proposed rules, and notices of Federal agencies and organizations are documented. In addition, executive orders and other crucial presidential documents are encompassed in the register. Initially, all the rules proposed were made available in the FR for availing public comments, and the finalized rule will be documented in the Code of Federal Regulations (CFR). After the respective modifications, if any, according to public and professional comments, the final regulations will be placed

I. Jagadeeswaran (✉)
Department of Biological Sciences, Southern Methodist University, University Park, TX, USA

N. Palani
National Reference Laboratory, National Institute for Research in Tuberculosis, Chennai, Tamil Nadu, India

G. Lakshmanan
Department of Anatomy, Asan Memorial Dental College and Hospital, Chengelpetu, Tamil Nadu, India

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_12

or codified into the printed edition of the Code of Federal Regulations (CFR) on an annual basis [1, 2]. Specific website for finding recently published FR's is Regulations.gov [3].

(c) *Code of Federal Regulations (CFR)*

The CFR is a codification where executive departments and agencies of the federal government publish the general and permanent rules in the FR [4]. The CFR was categorized into 50 title heads which epitomize broad areas subject to Federal regulation [5]. The highly important title of CFR is Title 21 Parts 800-1299 in which most of the FDA's medical device and radiation-emitting product regulations were comprised. The CFR codifies final regulations of various aspects of design, clinical evaluation, manufacturing, packaging, labeling, and postmarketing surveillance of medical devices. Regulations addressing standards and product reports implicating radiation-emitting products were addressed in CFR [1]. Various fields of products are categorized into the parts as mentioned in Table 1.

(d) *Electronic Code of Federal Regulations (e-CFR)*

The e-CFR is a current updated version of CFR, which is an unofficial editorial compilation of CFR material and FR amendments produced by the national archives and Records Administration's Office of the Federal Register (OFR) and the Government Printing Office. However, it is an official legal edition of the CFR. On a daily basis, the new materials will be updated by the OFR in the e-CFR. The current update status appears at the top of all e-CFR webpages [6].

2 FDA-CFR Title 21-Food and Drugs: Parts 800 to 1299

Title 21 CFR-FDA Parts 800 to 1299 were comprising of many essential regulations of medical devices and radiation emitting products [7]. The parts from 800 to 898 related to medical devices and their responsibilities were tabulated [7] in Table 2.

In this chapter, we will discuss in detail all the parts pertinent to medical devices in FDA-CFR Title 21.

Table 1 Respective parts of CFR dealing with specific products and responsibilities

S.No.	CFR parts	Products and responsibilities
1	1–99	Product jurisdictions, protection of human subjects, institutional review boards, etc.
2	100–799	Food, human and animal drugs, biologics, cosmetics
3	800–1299	Medical devices and radiation emitting products
4	1300–1499	Controlled substances

Table 2 Parts of FDA-CFR Title 21 which carry responsibilities of medical devices

S.No.	CFR Title 21 part no.	Products and responsibilities
1	800	General [8]
2	801	Labeling [9]
3	803	Medical device reporting [10]
4	806	Medical devices; reports of corrections and removals
5	807	Establishment registration and device listing for manufacturers and initial importers of devices
6	808	Exemptions from federal preemption of state and local medical device requirements
7	809	In vitro diagnostic products for human use
8	810	Medical device recall authority
9	812	Investigational device exemptions
10	813	[reserved]
11	814	Premarket approval of medical devices
12	820	Quality system regulation
13	821	Medical device tracking requirements
14	822	Postmarket surveillance
15	830	Unique device identification
16	860	Medical device classification procedures
17	861	Procedures for performance standards development
18	862	Clinical chemistry and clinical toxicology devices
19	864	Hematology and pathology devices
20	866	Anesthesiology devices
21	868	Cardiovascular devices
22	870	Dental devices
23	872	Ear, nose, and throat devices
24	874	Gastroenterology-urology devices
25	878	General and plastic surgery devices
26	880	General hospital and personal use devices
27	882	Neurological devices
28	884	Obstetrical and gynecological devices
29	886	Ophthalmic devices
30	888	Orthopedic devices
31	890	Physical medicine devices
32	892	Radiology devices
33	895	Banned devices
34	898	Performance standard for electrode lead wires and patient cables

2.1 Part 800: General Requirements for Specific Medical Devices [8]

All the preparations that were offered or intended for various ophthalmic purposes including contact lens solutions should be sterile, as per the informed medical opinion. If the ophthalmic preparations are nonsterile and fall below their avowed standard of purity or quality, then the preparation was considered as adulterated under Section 501(c) of the FD&C Act and may also be misbranded according to Section 502(j) of the Act. This ruling is applicable to all ophthalmic preparations which are considered as medical devices, i.e., contact lens solutions, by this regulation and for the ophthalmic preparations that are regulated as drugs by the regulation in 200.50 of FDA. The containers or individual carton used should be at the time of filling and shall be sealed to ensure that the contents cannot be used without destroying the seal. Multiple-dose ophthalmic preparations should be packed in containers either comprised of one or more suitable and harmless substances for inhibiting the growth of microorganisms or proper labelling with duration of use and necessary warnings to minimize contamination during use.

The FDA has an authority and responsibility under the FD&C Act, to establishment of a uniform national standard for tamper-resistant packaging and labelling of the over-the-counter (OTC) healthcare products including contact lens solution and/or tablet or other dosage form used for preparing ophthalmic solutions in accordance with 800.12 regulation of the FDA. Tamper-resistant packages have an indicator or a barrier to entry, which if breached or missing gives a visible evidence to the consumers that the tampering has occurred. This act improves the security of OTC products vulnerable to malicious adulteration and assure the safety and effectiveness of the product contained therein. The indicator or barrier is required to be distinctive by design or by using identification characteristics like pattern, name, registered trademark, logo, or picture in order to reduce the likelihood of substitution of the tamper-resistant feature. The term "distinctive by design" indicates that the package cannot be duplicated with commonly available materials or processes. A statement on the temper-resistant feature of the package is required to be placed in a way that it will be unaffected if the temper-resistant feature of the package is breached or missing. For example, statement on a bottle with a shrink band might say "For your protection, this bottle has an imprinted seal around the neck." All the ophthalmic solutions intended for retail sale that is not packaged in a tamper-resistant package and not labelled in accordance with this section of FDA regulation shall be considered adulterated under Section 501 and/or misbranded under Section 502.

Given the prevalence of human immunodeficiency virus (HIV), which causes acquired immunodeficiency syndrome (AIDS) and other blood-borne infectious diseases, FDA had started to regulate the quality of barrier devices such as medical gloves (i.e., surgeons' gloves and patient examination gloves) in order to control the risk of disease transmission in the healthcare context. Healthcare workers are recommended to wear medical gloves while handling blood or other body fluids, mucous membranes, or non-intact skin of all patients by the Centers for Disease Control and Prevention (CDC) to reduce the risk of transmission of blood- and

fluid-borne pathogens. Hence, FDA defined adulteration for patient examination and surgeons' gloves, as a means of assurance of the safety and effectiveness of the devices through this regulation. FDA collects sample from lots of medical gloves based on sample sizes, sample inspection levels, and acceptable quality levels (AQLs) as per International Standard Organization (ISO) 2859, "Sampling procedures for inspection by attributes." The lots of medical gloves that are sampled, tested, and rejected using the test methods such as general test method, leak test materials, and visual defects and leak test procedures are considered adulterated as per the 501(c)act. A lot of medical gloves is considered adulterated by FDA, if the number of defective gloves found in the tested sample meets or exceeds the applicable rejection number at 1.5 AQL for surgeon's gloves or the 2.5 AQL for examination of patient gloves.

Administrative Practices and Procedures
The medical devices intended for human use may be ordered detention in accordance with Section 704 of the FD&C Act by an authorized FDA representative, during an inspection, if the device is believed to be adulterated or misbranded, as defined in Section 201(h) of the Act. Administrative detention prevents the distribution or use of adulterated or misbranded medical devices to ensure public safety, until the FDA considers the action to be carried out concerning the devices and to initiate legal action, if appropriate. The medical devices ordered detention by FDA may not be used, moved, altered, or tampered during the detention period. The detention period is usually 20 calendar days. However, if the FDA determines that a greater period is required to seize the device or to evaluate the legal action required, the total detention period may not exceed 30 calendar days.

2.2 Part 801: General Labeling Provisions [9]

The label of the device in package form shall specify the name and place of business including city, State, and/or zip code of the manufacturer, packer, or distributor. If medical devices are manufactured or packed or to be distributed at a place other than the principal place of business of the manufacturer, packer, or distributor, then the label may specify the principal place of business, unless such statement would be misleading. The labelling of a device is considered misbranded, if it represents a false or misleading representation with respect to another device or food or cosmetic or a drug. If the label of the medical device includes a printed expiration date, date of manufacture, or any other date intended to be brought to the attention of the medical device user, the date should be presented in the following format: year (YYYY), followed by month (MM) and day (DD), i.e., 2020-11-03. Labelling of a device should also supply adequate directions for use, which ensures a layman can use a device safely for its intended purposes. Directions for use may be considered inadequate because of omission (either in whole or in part) or incorrect specification of:

(a) Statements on the conditions, purposes, or uses for the intended common use of medical device, for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising
(b) Quantity of dose for persons of different ages and different physical conditions
(c) Frequency of administration/application
(d) Duration of administration/application
(e) Time of administration/application, in relation to time of meals, time of onset of symptoms, or other time factors
(f) Route or method of administration or application
(g) Preparation for use, i.e., adjustment of temperature or other manipulation or process

These statements are required to appear on the label, and no exemption due to insufficiency of label space will be allowed by the FDA under Section 502(c)act. All the statements and other information on the label shall appear in English language or replaced by the predominant language of the territory, where the device is distributed.

Labeling Requirements for Unique Device Identifier

The label/package of every medical device shall bear a unique device identifier (UDI) that meets the requirements of Section 801.20 and Part 830 of the FDA. In addition to the UDI on label, each device must also carry a permanent direct marking UDI on the device itself, which can be identical to the UDI on the label of the device or a different UDI that can be used to distinguish the unpacked device from any device package containing the device. Direct marking of UDI on the device shall be exempted in conditions such as interference with the safety and effectiveness of the device, technologically not feasible for direct marking, and in single-use devices. Every UDI must be presented in both easily readable plain text and automatic identification and data capture (AIDC) technology. The UDI must include device identifier segment that conveys the information such as a lot or batch number, a serial number, a manufacturing date, and an expiration date. Stand-alone software regulated as a medical device must display its UDI as a readable plain-text statement either when the software starts or through a menu command or both. Once the UDI is assigned to a device, then National Health-Related Item Code (NHRIC) or National Drug Code (NDC) number may no longer be required to be on the label/package of the medical device. However, medical devices including class I device with a universal product code (UPC), single-usage devices, combination product with NDC numbers, and shipping containers are excepted from the requirement to bear a UDI according to Sections 801.30, 801.45, and 801.128(f)(2) of this FDA regulation. Section 801.55 provides a means to request an exception or alternative not provided by those provisions.

Labeling Requirements for Over-the-Counter Devices

The term principal display panel in over-the-counter devices in package form refers to the part of a label that is usually displayed, presented, shown, or examined under customary conditions of display for retail sale. The principal display panel should

accommodate and display all the mandatory label information with clarity and conspicuousness, and without obscuring designs, or crowding. In medical device packages with alternate principal display panels, the label information shall be duplicated on each principal display panel. To ensure uniform font size in declaring the contents of principal display panel for all packages, the term area of the principal display panel is defined as the area of the side or surface that bears the principal display panel. For example, in case of rectangular package, one entire side (product of height times the width of that side) shall be principal display panel side. The principal display panel shall bear a statement of identity of the commodity, followed by an accurate statement of the principal intended action(s) of the device. Statement of identity is one of the principal features of the principal display panel and shall be in size reasonably related to the most prominent printed information on such panels. The label of these over-the-counter medical device in package shall bear a declaration of the net quantity of contents expressed in terms of weight, measure, numerical count, or its combination. All over-the-counter devices containing or manufactured with chlorofluorocarbons, halons, carbon tetrachloride, methyl chloride, or any other class I ozone-depleting substance designated by the Environmental Protection Agency (EPA) shall carry a warning statement. In accordance with the requirements of 40 CFR part 82, this warning statement should be legible, prominent, and conspicuous on the product, its immediate container, its outer packaging, or other labeling to be easily read and understood by consumers.

Exemptions from Adequate Directions for Use

Devices with potentiality for harmful effect, or its common method of use known to ordinary individual or requires collateral measure such as supervision of a practitioner licensed by law for its use, are exempted for the requirement of "adequate directions for use" in the label. Medical devices used for processing or repacking in the manufacture of another drug/device or as in vitro diagnostic product (use in diagnosis of disease) or shipped or sold to persons regularly and lawfully engaged in teaching, law enforcement, research, and analysis, or any device held by the Strategic National Stockpile, shall be exempted from Section 502(f)(1) of the FDA Act, if the device meets the following conditions:

(a) If the device is in the possession of a person or his employees or agents manufacture, transportation, storage, or wholesale or retail distribution of such device; or a practitioner, such as physicians, dentists, and veterinarians, licensed by law to use or order the use of such device.
(b) Is sold only to or on the prescription or for use by a licensed practitioner in the course of his professional practice.
(c) Label of the medical device (except surgical instruments) bears symbol "Rx only" or "℞ only" or caution statement to restrict the sales of the device by or on the order of a state law licensed practitioner; and a method of its use or application.
(d) Labeling on or within the package of the dispensed medical device should bear the information for use, including indications, effects, routes, methods, frequency, and duration of administration, and any relevant hazards, contraindica-

tions, side effects, and precautions for the purpose it's advertised or represented.

(e) All the labelling bearing the information for use of the device also bears the date of issuance or the date of latest revision of such labelling.

2.3 Part 803: Medical Device Reporting [10]

This part delineates the requisites for medical device reporting to the facilities where the device will be used, to manufacturers, importers, as well as distributors. The device user facility should register and notify the deaths and serious injuries contributed and suspected from the device usage. Device malfunctions and adverse events should be recorded and maintained. These ensures the devices are not adulterated or misbranded and are used safely and effectively. The distributor must also maintain the records of incidents, though they may not report the same. Any report submitted can be disclosed to the public in accordance with §803.9. It includes FDA report of telephone records. But trade secrets, confidential commercial and financial information, personal medical information like serial numbers of implanted devices, and names and information identifying a third party that voluntarily submitted an adverse event report can all be deleted before public disclosure.

Reporting Requirements That Applies to Device User Facility

The device user facility must submit individual adverse events within 10 working days including device-related deaths and serious injuries to the manufacturer and FDA. The importer should submit annual report on adverse events, device-related deaths, or serious injuries to FDA and the manufacturer. Any device-related malfunction should be reported to the manufacture, and the manufacturer should report about individual adverse events in 30 calendar days. Any reportable event requiring remedial action or upon a written request over any reportable event and to submit supplemental reports to a submitted initial report can be submitted within 5 working days. The manufacturer or importer must report individual adverse events in electronic format in accordance with §803.11.

The manufacturer or importer must report initial, supplemental, or follow-up reports in electronic format that FDA can process, review, and archive. User facilities must submit their reports and additional information in electronic format in English to FDA as "User Facility Report" or "Annual Report." Confrontations with public health emergencies can be brought to FDA's attention at 301-796-8240 or toll free at 866-300-4374, followed by the submission of an email to *emergency.operations@fda.hhs.gov*. When further additional information is required, the FDA will notify in writing about the required additional information if protection of the public health requires additional or clarifying information for medical device reports submitted and in cases when the additional information is beyond the scope of FDA reporting forms or is not readily accessible to FDA. All such request will state the reason or purpose for the information request, specify the due date for submitting

the information, and clearly identify the reported event(s) related to our request. Verbal request for additional information will be followed by request in writing. Any report or information submitted to FDA following the written request does not necessarily reflect a conclusion that the device, or manufacturer or their employees, caused or contributed to the adverse event.

Requirements for Developing, Maintaining, and Implementing Written MDR Procedures

Any user facility, importer, or manufacturer must develop, maintain, and implement written MDR procedures for internal systems that provide for identification, communication, and evaluation of events with a standardized review process and timely transmission of the report to the FDA or manufacturers with evaluation of reportable event including all medical device reports and information submitted to manufacturers or FDA along with evaluated information for annual reports and systems that ensure access to information that facilitates timely follow-up and inspection by the FDA.

Requirements for Establishing and Maintaining MDR Files or Records

A user facility, importer, or manufacturer must establish and maintain MDR event files and keep accessible with all information in possession with copies of report submitted and copies of all electronic acknowledgements from FDA and permit any authorized FDA employee to access and verify the same. An MDR file has to be retained for 2 years from the date of event. A device distributor must maintain a device complaints records of all incident information related to identity, quality, durability, reliability, safety, effectiveness, or performance of a device along with distributor evaluation of the same at least for 2 years even if the distributor no longer distributes the device.

Exemptions, Variances, or Alternative Forms of Adverse Event Reporting Requirements

A licensed practitioner is an individual, who manufactures devices intended for use in humans solely for this person's use in research or teaching and not for sale. Dental laboratories or optical laboratories are exempted from adverse event reporting. A manufacturer, importer, or user facility, may request an exemption or variance from any or all of the reporting requirements, with the information necessary to identify the device and a complete statement of the request for exemption, variance, or alternative reporting along with proper justification. However, this has to be granted by FDA and can be revoked at any time.

Applicable Requirements for Individual Adverse Event Reports

A health professional or consumer or any other entity can submit their voluntary reports to the FDA regarding their devices or products using form FDA 3500A including a mandatory report in written form. An e-submission from a user facility, importer, or manufacturer must have information about the patient, the event, the device, and the "initial reporter" along with information from blocks G and H as well as including any corrected or missing information. Within 10 days of an adverse event, the user facility should report to the manufacturer or to the FDA. The

manufacturer should report to the FDA in 30 calendar days. All the adverse reporting codes to use with form FDA 3500A can be obtained from The MedWatch Medical Device Reporting Code Instruction Manual available at https://www.fda.gov/medical-devices/mandatory-reporting-requirements-manufacturers-importers--and-device-user-facilities/mdr-adverse-event-codes. Any additions and modifications to the existing codes will be made available to all reporters from time to time. Multiple information of the same patient and same event can be submitted as a single report. If the information received is determined as erroneous, it need not be reported by user facility, importer, or manufacturer. However, the documentation of these reports would be mentioned in MDR files for the time periods specified in §803.18. Any reporting to the wrong manufacturer or importer should be reported to the FDA by the receiver of such report.

User Facility Reporting Requirements

For a user facility, reports of death and serious injury must be submitted in 10 days to the manufacturer and the FDA as required by §803.32. Reports sent to the Agency must be submitted in accordance with the requirements of §803.12 (b). This should include information found in documents possessed by the user facility and any information that becomes available as a result of reasonable follow-up within the facility. An annual report should be submitted on form FDA 3419 by January 1 of each year and should include CMS provider number used for medical device reports, reporting year, name and complete address, total number of reports attached, date of the annual report, and details of the person reporting, and all information of the reportable events should be noted.

Importer Reporting Requirements

Reports of deaths and serious injuries as well as reports of malfunctions should be reported to the FDA. Reports should be prepared and submitted in 30 calendar days. Importer should correspond generally to the format of form FDA 3500A with the necessary patient information, adverse event or product problem, all necessary device information, and initial reporter information as well as the importer information.

Manufacturer Reporting Requirements

In case of a suspected death or grievous injury caused by the device or upon any malfunction of the device, it should be reported within 30 calendar days. All sorts of information obtained by contacting a user facility, importer, or other initial reporter as well as by analysis, testing, or other evaluation of the device should be submitted to the FDA. It is the responsibility of the manufacturer to get and submit all the details and also to investigate each event and evaluate the cause of the event. All patient information, complete adverse event or product malfunction information, detailed device information, manufacturer details, and initial reporter information are to be furnished by the manufacturer in the form FDA 3500A from Block A to Block H. An MDR reportable event necessitates remedial action to prevent an unreasonable risk of substantial harm to the public health, and upon receiving a written request for the submission of a 5-day report from the FDA, a manufacturer

should submit a 5-day report within 5 working days. It can be extended upon a written interest and is in the interest of the public. Every foreign manufacturer whose devices are distributed in the United States shall designate a US agent to be responsible for reporting. The US-designated agent accepts responsibility for the duties that such designation entails. US-designated agents of foreign manufacturers are required to report to the FDA, conduct and obtain necessary information on investigation and evaluation of the event, forward MDR complaints to the foreign manufacturer, and maintain documentation of this requirement and complaint files and register.

2.4 Part 806: Medical Devices, Reports of Corrections and Removals [11]

This part implements the provisions of Section 519(g) of the Federal Food, Drug, and Cosmetic Act that mandates device manufacturers and importers to report on any of the device corrections and removals as well as to maintain records of those corrections and removals. However, actions taken by manufacturers to enhance the performance or quality of a device which do not pose a health threat, market withdrawal of the device, routine servicing, and stock recovery can be exempted from reporting requirements.

Reports of Corrections and Removals
For any correction or removal of a device, the device manufacturer or importer should submit a written report. This can be aimed at reducing a health risk posed by the device or to remedy a violation of the act caused by the device, and it should be done within 10 working days of the initiation of the correction or removal. In the submitted report, the manufacturer or importer should include the 7-digit registration number of the entity responsible for submission of the report of corrective or removal action (if applicable); the month, day, and year that the report is made; a sequence number (i.e., 001 for the first report, 002 for the second report, 003, etc.); and the report-type designation "C" or "R". Firms that do not have a 7-digit registration number may use seven zeros followed by the month, date, year, and sequence number (i.e., 0000000-6/1/97-001-C for corrections and 0000000-7/1/97-001-R for removals). Reports received without a 7-digit registration number will be assigned a 7-digit central file number by the district office reviewing the reports. It should also include the details of the manufacturer, details of the event giving rise to the information reported, and the corrective or removal actions that have been done and are expected to be taken, details of the production including date, no. of devices produced, details of all consignees of the devices, and how many was distributed by each of them. A copy of all communications regarding correction or removal should be added to the report. To amend any submitted report, it should be done within 10 working days of initiating the extension of the correction or removal and amended by submitting an amendment citing the original report number assigned.

Records of Corrections and Removals Not Required to Be Reported
All correction or removal of a device that is not required to be reported to the FDA should be maintained as a separate record. Such records shall contain details of the device including a unique device identifier (UDI) or the device identifier, universal product code (UPC), model, catalog, or code number of the device and the manufacturing lot or serial number of the device or other identification number and description of reported events and justification for not reporting the event. All communications toward this should be recorded. This should be maintained for a period of 2 years beyond the expected life of the device. Upon request of an officer or employee designated by the FDA and under Section 704(e) of the Act, each device manufacturer or importer should allow them to have access to, and to copy and verify, such records and reports maintained toward the cause. All reports under this part are available for public disclosure, but before disclosing, the FDA will remove any information that constitutes trade secret or confidential commercial or financial information as well as any personnel, medical, or similar information, including the serial numbers of implanted devices, which would constitute a clearly unwarranted invasion of personal privacy. However, if a patient requests all the information in the report concerning that patient, it will be released by the FDA.

2.5 Part 807: Establishment Registration and Device Listing for Manufacturers and Initial Importers of Devices [12]

Any distribution of a device intended for human use which is held or offered for sale is termed as commercial distribution (except of those internally transferred/exempted/introduced before May 28, 1976), and the place of business/one general physical location where the device is manufactured/assembled/processed is the establishment. The designated person for annual registration of the establishment and contact person with the FDA for device listing, maintenance, and submission of records and corresponds between FDA and owner/operator is the office correspondent.

Procedures for Device Establishments
(a) *Who Must Register and Submit a Device List?*

The term "device" can be used for all in vitro diagnostic products and in vitro diagnostic biological products. An owner or operator shall register its name, places of business, all the establishments while listing. In addition, registration shall pertain to any person who initiates or develops specifications for a device, makes a device on behalf of specifications provided, repackages or relabels a device, reprocesses a single-use device that has previously been used on a patient, and the initial importer.

(b) *How to Register Establishments and List Devices?*

Owners or operators of establishments must electronically register the device of interest with initial establishment information, updates to registration information,

initial device listing information, and updates to device listing information (including updates to reflect the halt of commercial distribution of previously listed device). If electronic submission is not possible, a waiver may be requested for reasonable explanations by providing information on name and address of device establishments and information about the company and reason for request.

(c) *Times for Establishment Registration and Device Listing*

If the owner or operator of an establishment is newly entering the device in listing, they shall register within 30 days after entering into an operation and submit the device listing information at that time. If already registered, they shall review and update any changes that were not previously reported. Failure to submit any required information on time will be noted as "failed to register" or "failed to list," and the list of device may not be put on the FDA website till complete submission.

(d) *Information Required for Device Establishment Registration and Device Listing*

Registration information includes the name, mailing address of the device establishment, website address, contact details of the owner, establishment, and all trade names used by the establishment. The listing shall include all officers, directors, and partners to furnish to FDA upon request. The official correspondent would serve as a point of contact with FDA on all matters relating to the registration of device establishments. He/she would be responsible for providing the FDA all required registration and listing information electronically, receiving all correspondence from FDA, and supplying the list of officers/directors/partners upon request. The information required for each device listed includes current registration number, name of each establishment, product code of each device, proprietary or brand name(s), FDA-assigned premarket submission number of approved application, and list of each activity or process that is conducted on or done to the device at each establishment.

(e) *Additional Listing Information*

Each owner or operator shall maintain a historical file containing labeling and advertisements in use on the date of initial listing, location of files including currently existing records, historical files, copy of certification, and disclosure statements. Upon specific request, each owner or operator shall provide a copy of all labelling for the device, a copy of all advertisements, label and package insert of the device, a statement of the basis to determine the device is not a restricted one, and list of all distributors for whom the device is manufactured.

(f) *Updating Device Listing Information*

Updating of device listing information is required if an additional establishment begins to engage or if it begins performing another activity on or to the device or ceases to perform an activity on or the device that had previously been identified on the device listing. However, a new device listing is created if device is not currently listed by the owner or operator, if the device is a non-exempt one with new FDA premarket submission number, or if the device is imported or offered into United Sates from a foreign establishment. A device listing is discontinued if all devices

under an exempt product code have been discontinued or all devices associated with an FDA premarket submission number have been discontinued.

(g) *Summary of Requirements for Owners or Operators Granted a Waiver*

An owner/operator who has been granted a waiver from electronic filing must send a letter containing all of the registration and listing information to the Imports and Registration and Listing Team, FDA, and shall update their establishment registration and device listings annually during the period between October 1 and December 31 of each fiscal year. Failure to submit any required information on time will be noted as "failed to register" or "failed to list," and the list of devices may not be put on the FDA website till complete submission.

(h) *Notification of Registrant*

The FDA will assign each device establishment a registration number after verifying the initial registration information that has been submitted along with an identifying number for the owner/operator. Both these numbers will be sent to official correspondent by email or by post. Validation of registration and device listing does not ensure the legal qualification of registration until further scrutinization.

(i) *Public Availability of Establishment Registration and Device Listing Information*

Establishment registration and device listing information is made available for public inspection with exception of certain information including contract manufacturers, contract sterilizers, private label manufacturers, proprietary or brand names, and FDA-assigned listing numbers.

(j) *Misbranding by Reference to Establishment Registration or to Registration Number*

Any representation intended to create an impression of official approval because of registration approval is misleading and may be misbranded.

Procedures for Foreign Device Establishments

(a) *Establishment Registration and Device Listing for Foreign Establishments*

Any establishment in a foreign country importing or offering the device into the United States shall undergo electronic device registration, and the official correspondent of the foreign establishment shall facilitate communication with the FDA on behalf of the owner or operator. Each foreign establishment shall designate only one agent in the United States to act as an official correspondent who resides in the United States and shall maintain a place of business. The correspondent shall assist the FDA by responding to all questions raised, for onsite inspections, and by reporting changes within 10 business days of the change.

(b) *Identification of Importers and Persons Who Import or Offer for Import*

Upon initial registration, annually at time of any changes, each foreign establishment is required to register through FDA electronic device registration and listing system with details of importers of persons who imports or offers for import.

(c) *Exemptions*

The following classes of persons are exempted from registration by the Commissioner of Food and Drugs: a manufacturer of raw materials or components to be used for the device; a manufacturer of a device solely for veterinary purposes or chemical reagents; licensed practitioners, pharmacies, or surgical supply outlets; persons who manufacture, prepare, and propagate devices solely for use in research, teaching, or analysis; and carriers of devices or who dispense devices to consumers.

Premarket Notification Procedures

(k) *When a Premarket Notification Submission Is Required*

Each person who has to register their establishment must submit a premarket notification submission to the FDA at least 90 days before initiating the introduction of commercial distribution of a device intended for human use. This includes all devices being introduced into commercial distribution for the first time or reintroduced with significant changes or modifications in designs, components, method of manufacture, or intended use.

(l) *Exemption from Premarket Notification*

A custom device is exempted from premarket notification requirements if it is intended for use by a patient named in the order of the physician or dentist or solely for use by a physician or dentist or if a distributor who places a device into commercial distribution for the first time under his own name and a repackager who places his own name on a device if the premarket notification submission was filed by another person or if the device was in commercial distribution before May 28, 1976.

(m) *Information Required in a Premarket Notification Submission*

The premarket notification submission shall include the device name, establishment registration number, class of the device, statement of classification, action taken by the person required to register to comply with the requirements, proposed labels, labeling, advertisements, a statement indicating the device is similar or different from other products if any, and a financial certification or disclosure statement or both. The submission should be supported by clinical investigations conducted inside or outside the United States, statement that the submitter believes to best of his/her knowledge about the truthful, and accurate information provided. If any information is requested by the Commissioner, the same has to be submitted promptly, and failure of submission within 30 days will make the premarket notification withdrawn.

(n) *Format of a Premarket Notification Submission*

Each premarket notification submission shall be submitted to respective sections like Center for Devices and Radiological Health or Center for Biologics Evaluation and Research, and all inquiries should be sent as a single version electronically, separately for each product with the designated "510|(k) notification in the cover letter."

(o) *Content and Format of a 510(k) Summary*

A 510(k) summary shall contain details to provide an understanding of the basis for a determination of substantial equivalence, and it shall include the submitter's name, address, and contact details; name of the device trade or proprietary name (if applicable); identification of the legally marketed device to which the submitter claims equivalence; description of the device, its functioning, scientific concepts, and physical and performance characteristics; and a statement of the intended use of the device that is the subject of the premarket notification submission. In addition to it, it shall also include a brief discussion of clinical and nonclinical tests submitted, conclusions drawn from these tests, and an exclusive summary with any other information necessary to be attached.

(p) *Content and Format of a 510(k) Statement*

A 510(k) statement signed by the certifier shall state that "I certify that, in my capacity as (the position held in company by person required to submit the premarket notification, preferably the official correspondent in the firm), of (company name), I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR 20.61."

(q) *Format of a Class III Certification*

A class III certification submitted as a part of a premarket notification signed by the certifier shall state that "I certify in my my capacity as (position held in company), of (company name), that I have conducted a reasonable search of all information known or otherwise available about the types and causes of safety or effectiveness problems that have been reported for the (type of device). I further certify that I am aware of the types of problems to which the (type of device) is susceptible and that, to the best of my knowledge, the following summary of the types and causes of safety or effectiveness problems about the (type of device) is complete and accurate."

(r) *Confidentiality of Information*

The FDA will disclose publicly whether the device is on the market and whether the person submitting the premarket notification submission has disclosed his intent to market the device, analyses, or not. But FDA shall not disclose the existence of premarket notification submission for a device that is not in the market or if requested to hold the intent as confidential commercial information up to 90 days from the date of the receipt of submission.

(s) *Misbranding by Reference to Premarket Notification*

Submission of a premarket notification and subsequent determination by the Commissioner that the device intended is substantially equivalent to a device in the

commercial distribution. However, any representation that creates an impression of official approval of a device because of complying with the premarket notification regulation is misleading and can lead to misbranding.

(t) *FDA Action on a Premarket Notification*

After review of premarket notification, FDA will an issue an order declaring the device to be substantially equivalent/not equivalent to a legally marketed device, request more information, withhold decision until certification or disclosure statement is submitted, or inform the applicant that the premarket notification is not required. FDA will determine whether the device of interest is substantially equivalent to a predicate device if it has the same technological characteristics or if the device is as safe and as effective as a legally marketed device.

2.6 Part 808: Exemptions from Federal Preemption of State and Local Medical Device Requirements [13]

This part sets forth the procedure for submission, review, and approval of applications for exemptions from Federal preemption of State and local requirements applicable to medical devices under Section 521 of the FDA Act. The FDA is responsible for determining whether a State or local requirement is equal or substantially identical or different or in addition to the Federal requirements with respect to a device. However, if any State or political subdivision whose requirements relating to a device are preempted in accordance with Section 521(a), they may petition the Commissioner of the FDA for exemption from preemption.

(a) Section 521(a) of the Act prescribes special provisions that after May 28, 1976, no State or political subdivision of a State may establish or continue in effect any requirement with respect to a medical device intended for human use having the force and effect of law, which is different from, or in addition to, any requirement applicable to such device under any provision of the act and which relates to the safety or effectiveness of the device or to any other matter included in a requirement applicable to the device under the Act.
(b) In accordance with Section 521(b), the Commissioner of the FDA may, upon application by a State or political subdivision, allow imposition of a requirement which is different from, or in addition to, any requirement applicable under the Act to the device (and which is thereby preempted) by promulgating a regulation.

Exemption Procedures
A signed letter from an authorized State or political division in accordance with §808.20 (if not, they will be returned for corrections) may request exemption to the Commissioner of the FDA. For each requirement for which an exemption is sought shall include all the information and explanation to justify the requirement. Upon receipt of the application meeting the requirements of §808.20, the Commissioner shall review such application and will issue in the FEDERAL REGISTER a

proposed regulation to either grant or deny an exemption from preemption for each requirement. An exemption from preemption in accordance with §808.25 shall remain effective until the Commissioner revokes such exemption.

2.7 Part 809: In Vitro Diagnostic Products for Human Use [14]

In vitro diagnostic products are those reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. Data and information submitted shall be treated as confidential by the FDA and any person to whom the data and information are referred.

Labelling for In Vitro Diagnostic Products
The label for an in vitro diagnostic product shall have its proprietary name, established name, and its intended use. For reagents, its established name, its source, and measure of activity should be labelled. A statement of warning and precautions along with a statement "For In Vitro Diagnostic Use" should be added. Any other limiting statement can also be added and shall bear the symbol statement "Rx only" or "℞ only" or the statement "Caution: Federal law restricts this device to sale by or on the order of a ___", the blank to be filled with the word "physician," "dentist," "veterinarian," or the descriptive designation of any other practitioner licensed by the law of the State in which the practitioner practices to use or order the use of the device.

Appropriate storage instructions including temperature, light, humidity, and other factors should be added. For products requiring manipulation, such as reconstitution and/or mixing before use, appropriate storage instructions shall be provided for the reconstituted or mixed product which is to be stored in the original container. The basis for such instructions shall be determined by reliable, meaningful, and specific test methods. An expiration date, net quantity of contents, and a statement of an observable indication of an alteration of the product can be added for a reagent. The details of the manufacturer and lot number with ability to tracing individual units can be added.

Labelling accompanying each product should also have all the abovementioned details.

Summary and explanation of the test including a short history of the methodology with pertinent references and a balanced statement of the special merits and limitations of this method or product should also be added. In case of reagents, established names and a statement indicating the presence of and characterizing any catalytic or nonreactive ingredients, e.g., buffers, preservatives, and stabilizers, can be added. A statement of warning and precautions with a statement "For In Vitro

Diagnostic Use" should be added. Adequate instructions for reconstitution, mixing, dilution, etc. should also be included. In case of instruments, use or function, installation procedures and special requirements, principles of operation, performance characteristics and specifications, operating instructions, calibration procedures including materials and/or equipment to be used, operational precautions and limitations, hazards, and service and maintenance information should be included.

In case of a specimen collection, a description of special precautions regarding specimen collection including special preparation, additives, preservatives, known interfering substances, recommended storage, and handling details can all be included. In the case of a procedure, a step-by-step outline of recommended procedures from reception of the specimen to obtaining results with stressing anything that may improve the precision and accuracy can be added. List of materials provided, list of materials required but not provided, description of reagents quantity needed, and a statement on the stability of the final reaction and other details of calibration and quality control procedures should be stated. The procedure for calculating the results in a detailed manner along with limitations of the procedure covering the known extrinsic factors and interfering substances, with the expected values and a final note on bibliography, should all be included. Apart from this, other standard labelling norms should be followed.

Exceptions or Alternatives to Labeling Requirements for In Vitro Diagnostic Products for Human Use Held by the Strategic National Stockpile

The appropriate FDA Center Director may grant an exception or alternative, if a strategic National Stockpile official posts a written request for an exception or alternative. The center director may grant an exception or alternative described in paragraph (a) of this section on his or her own initiative with the identity of the thing explaining why compliance with such labeling provision(s) could adversely affect the safety, effectiveness, or availability of the specified lots, batches, or other units of the in vitro diagnostic product for human use that are or will be held in the Strategic National Stockpile with proposed safeguards or conditions. A grant of an exception or alternative under this section will include any safeguards or conditions deemed appropriate by the Center Director to ensure that the labeling of the product subject to the exception or alternative includes the information necessary for the safe and effective use of the product, given the anticipated circumstances of use. For a Premarket Approval Application (PMA)-approved in vitro diagnostic product for human use, the submission and grant of a written request under this section satisfy the provisions relating to submission of PMA supplements.

Restrictions on the Sale, Distribution, and Use of Analyte Specific Reagents

In vitro diagnostic products shall be manufactured in accordance and compliance with the good manufacturing practices requirements. Analyte specific reagents (ASRs) are restricted devices and may be only sold to clinical laboratories regulated under the Clinical Laboratory Improvement Amendments of 1988 and to Organizations that use the reagents to make tests for purposes other than providing diagnostic information to patients and practitioners.

Advertising and promotional materials for ASRs should include the statement for class I exempt ASRs, “Analyte Specific Reagent. Analytical and performance characteristics are not established,” and for class II or III ASRs, “Analyte Specific Reagent. Except as a component of the approved/cleared test (name of approved/cleared test), analytical and performance characteristics are not established,” and should not make any statement on its analytical and clinical performance.

The laboratory that develops an in-house test using the ASR shall inform the ordering person of the test result by appending to the test report the statement: “This test was developed and its performance characteristics determined by (Laboratory Name). It has not been cleared or approved by the U.S. Food and Drug Administration.” This statement would not be applicable or required when test results are generated using the test that was cleared or approved in conjunction with review of the class II or III ASR.

Restrictions on the Sale, Distribution, and Use of OTC Test Sample Collection Systems for Drugs of Abuse Testing

Over-the-counter (OTC) test sample collection systems for drugs of abuse testing are restricted devices. Sample testing should be performed in a laboratory using screening tests that have been approved, cleared, or otherwise recognized by the FDA as accurate and reliable for the testing of such specimens for identifying drugs of abuse or their metabolites. The laboratory where the tests are performed should have been a recognized one and proven to have adequate capability to perform integrity checks for possible adulterations in the biological samples.

2.8 Part 810: Medical Device Recall Authority [15]

This part of the regulation describes the procedures that the FDA will follow in exercising its medical device recall authority under Section 518(e) of the FDA Act. If, after providing the appropriate person with an opportunity to consult the agency, FDA finds that there is reasonable probability that the device intended for human use would cause serious, adverse health consequences or death, the agency may issue a notification for immediate order to:

(a) Cease the distribution of the device
(b) Notify and instruct the health professionals and the device user facilities to cease the use of the device

A written request for regulatory hearing under §810.11 may be submitted to the FDA for review of cease distribution and notification order. Such requests shall be addressed to agency employee identified in the order and shall submit within the stipulated timeframe under §16.22(b) (usually 3 working days from receipt of cease order) specified by the FDA. Within the 15 working days of receipt of the written request, the agency shall provide written notification (a statement) on its decision to affirm, modify, vacate, or amend the order to the requestor. If a regulatory hearing

or agency review of the order is not requested, or within 15 working days of denying a request for a hearing, or within 15 working days on completion a regulatory hearing under §810.11, or within 15 working days of receipt of a written request for review of a cease distribution and notification order under §810.12, then the FDA shall amend the order to require a recall or a mandatory recall of the device within 15 working days of issuance of a cease distribution and notification order. A descriptive listing of each new mandatory recall issued will be available to the public in the weekly FDA Enforcement Report by the agency.

If cease distribution and notification order or a mandatory recall order is issued, then the person mentioned in the order should submit a periodic report (as specified in the order) to the FDA on his progress in complying with the order. On compliance with order, the person mentioned in the cease distribution and notification order may submit a written request to the FDA for termination of the order. After assessing the person's progress in complying with the order, FDA may deny or grant the termination of device recall order within 30 working days of its receipt.

2.9 Part 812: Investigational Device Exemptions [16]

Discovery and development of useful devices intended for human use is encouraged, and optimum freedom is given for scientific investigators for this purpose. In conduct of clinical investigations of devices, approved investigational device exemption (IDE) permit is given to such devices which otherwise would be subjected to comply all the performance standard or premarket approval to be shipped lawfully. An IDE approved under or considered approved exempts a device from the requirements of the following sections of the Federal Food, Drug, and Cosmetic Act and the regulations issued from the agency.

Applicability

- General: In this part, all the clinical investigations of devices which determine safety and effectiveness will be proved except the exempted investigations.
- Abbreviated requirements: The following are categories of investigations to get approval of applications for IDEs:

  (i) An investigation of a device including labelling, IRB approval, a brief explanation of why the device is not a significant risk device, documents proving the collection of informed consent unless documentation is waived by an IRB, and maintenance of records

- Exempted investigations: This part does not apply to investigations of the following devices:

  (a) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time

(b) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, the FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976
(c) A diagnostic device, if the sponsor complies with applicable requirements and if the testing is noninvasive, which does not require an invasive sampling procedure that presents significant risk, does not by design or intention introduce energy into a subject, and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure
(d) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not the purpose of determining safety or effectiveness and does not put subjects at risk
(e) A device intended solely for veterinary use
(f) A device shipped solely for research on or with laboratory animals and labeled in accordance animal research caution labelling format
(g) A custom device as per Federal Food, Drug, and Cosmetic Act unless the device is being used to determine safety or effectiveness for commercial distribution

Labeling of Investigational Devices

The contents shall bear label with information including name, place of business of manufacturer, packer or distributor, and quantity of contents, with CAUTION notice with following statement if appropriate "CAUTION-Investigational device. Limited by Federal (or United States) law to investigational use." Other labels shall also be displayed for describing relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Labeling of an investigational device shall not bear any statement that is false or misleading in any particular and shall not represent that any device is safe or effective for the purpose for which it is being investigated. Any device shipped solely for research on or with laboratory animals shall bear on its appropriate detailed label.

Prohibition of Promotion and Other Practices

A sponsor, investigator, or any person shall not promote or test market an investigational device, until after FDA has approved the device for commercial distribution. They shall not commercialize by charging the subjects or investigators for a device a price larger than that necessary to recover costs of manufacture, research, development, and handling. They shall not unduly prolong an investigation or represent it as safe or effective for the purposes for which it is being investigated.

Waivers

A sponsor shall request the FDA to waive any requirement, and this request with supporting documentation may be submitted separately or as a part of an application. FDA may grant a waiver of any requirement if it is not required by act or is unnecessary to protect the rights, safety, or welfare of human subjects. Any requirement shall continue to apply unless and until FDA waives it.

Import and Export Requirements

A person who imports or offers for importation an investigational device shall be the agent of the foreign exporter with respect to investigations of the device and shall act as the sponsor of the clinical investigation or ensure that another person acts as the agent of the foreign exporter and the sponsor of the investigation. A person exporting an investigational device shall obtain FDA's prior approval before proceeding.

Address for IDE Correspondence

All applications, reports, request for waiver, request for import or export approval, or any other correspondence must be sent to the appropriate address mentioned in the official website with a submission title mentioned on the outside wrapper.

Application and Administrative Action

1. Submission: A sponsor shall submit an application to the FDA if the sponsor intends to use a significant risk device in an investigation or to conduct an investigation that involves an exception from informed consent or if FDA notifies that an application is required for an investigation. FDA needs to approve an application from the sponsor to conduct an investigation after which sponsor shall submit a signed "Application for an investigational Device Exemption" (IDE application), with accompanying materials in electronic format. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier.
2. The investigational plan shall include purpose, protocol, risk analysis, description of device, monitoring procedures, labeling, consent materials, IRB information, and other additional records and reports.
3. The report of prior investigations will include general reports of all prior clinical, animal, and laboratory testing along with specific contents including bibliography of all publications, published or unpublished adverse information, nonclinical laboratory studies, and data from clinical investigations.
4. Acceptance of data from clinical investigations conducted outside the United States will need additional conditions to be met based on good clinical practice (GCP) which includes review, independent ethics committee (IEC), and supporting information.
5. FDA action on applications: FDA will notify the sponsor in writing of the date it receives an application. FDA shall provide a written determination 30 days after FDA receives the IDE or earlier. DA takes 30 days' time to approve an investigation as proposed, approve with modifications, or disapprove it or withdraw approval an application. FDA shall consider the use of an investigational device under category "treatment IDE" to facilitate the availability of promising new devices to desperately ill patients as early as possible. FDA will not disclose the existence of IDE unless its existence has been previously been publicly disclosed or acknowledged until approval of device. FDA will make a detailed summary of information concerning the safety and effectiveness of the device after approval upon request.
6. Supplemental applications: (a) Changes in investigational plan shall include changes requiring prior approval, changes effected for emergency use, changes

effected with notice to FDA within 5 days (developmental changes, changes to clinical protocol, definition of credible information, notice of IDE change), changes submitted in annual report, or IRB approval for new facilities.
7. Treatment use of an investigational device: FDA shall consider the use of an investigational device under a treatment IDE if the device is intended to treat or diagnose a serious or immediately life-threatening disease; no comparable or satisfactory alternative device or other therapy is available to treat or diagnose the stage of the disease.
8. Confidentiality of data and information will be maintained unless its existence has previously been publicly disclosed or acknowledged.

Responsibilities of Sponsors
Sponsors shall not begin investigation until both IRB and FDA have approved the application. The responsibilities of sponsors are the following:

(a) Selecting investigators and monitors
(b) Informing investigators
(c) Monitoring investigations

IRB Review and Approval
An IRB shall review and have authority to approve, require revisions on, or disapprove all investigations, and if there is no IRB or FDA finds IRB review is inadequate, a sponsor shall submit an application to FDA directly. IRB can demand an investigation for devices involving a significant risk through the sponsor prior to approval.

Responsibilities of Investigators
An investigator is responsible for ensuring a proper conduct of investigation as per the signed agreement. The conduct shall be according to investigational plan and FDA regulations, after obtaining informed consent, and they also will be liable for protecting the rights, safety, and welfare of subjects and for control of devices under investigation. The specific responsibilities of investigators include the following:

(a) Awaiting approval
(b) Compliance
(c) Supervising device use
(d) Financial disclosure
(e) Disposing of device

A clinical investigator can be disqualified if FDA has information that an investigator has deliberately failed to comply with the requirements or repeatedly submitted false information in any required report. In such cases, the Centre of Devices and Radiological Health, the Centre for Biologics Evaluation and Research, or the Centre for Drug Evaluation and Research will furnish a written notice on matter of complaint and offer to provide the investigator's explanation in writing or through an informal conference. If the explanation provided is accepted, disqualification

proceeding will be discontinued, otherwise will be examined with test articles to support his explanation.

Records and Reports (a) *Records*

- Investigator records: A participating investigator shall maintain all the correspondence with another investigator, an IRB, the sponsor, a monitor, or the FDA. They preserve the records of receipt, the use of device including the type and quantity of device, batch number or codes, and the name of all persons who received or used the device and details of units. He/she shall also hold records of each participant's case history, date and time of each use, exposure details, signed and dated consent forms, medical records, hospital charts, and nurses' notes.
- Sponsor records: A sponsor shall maintain all correspondence with another sponsor, a monitor, an investigator, an IRB, or the FDA. They record the shipment and disposition including the name and address of the consignee; type and quantity of device; date of shipment; batch number or code mark; details if any devices were returned to the sponsor, repaired, or disposed; and signed investigator agreements. They shall preserve records of name and intended use of device, objectives of the investigation, explanation of non-risky aspects of the device, statements of good manufacturing practice regulations, and notes of adverse device effects.
- Retention period: All the records of investigator or sponsor shall be maintained for a period of 2 years after the date on which the investigation is terminated or completed or the date that records are no longer required for purpose of supporting a premarket approval application.

(b) *Inspections*

A sponsor or an investigator shall permit authorized FDA employees, at fixed time and manner, to inspect the establishment where the devices/records are held (including sites where these are manufactured, packed, installed, used, or implanted). They shall permit FDA employees to inspect and copy all records related to this investigation, subjects, and the informed consents.

(c) *Reports*

- Investigator reports: An investigator shall prepare and submit complete, accurate, and timely reports including report of any unanticipated adverse effects, withdrawal of IRB approval, progress reports, deviations from the investigational plan, informed consents, and the final report.
- Sponsor reports: A sponsor shall prepare and submit complete, accurate, and timely reports including unanticipated adverse device effects, withdrawal of IRB approval, withdrawal of FDA approval, current investigator list, progress reports, recall and device disposition, final report, informed consent, and significant risk device determinations.

2.10 Part 814: Premarket Approval of Medical Devices [17]

The premarket approval (PMA) of medical devices applies to any class III medical device that was not on the market before May 28, 1976. The review process of premarket approval of medical devices facilitates the approval for those devices that have been shown to be safe and effective and that meets statutory criteria and approval and disapprove otherwise.

Confidentiality of Data and Information in a Premarket Approval Application (PMA) File
A PMA file includes all data and information submitted with or incorporated by reference in the PMA, any IDE incorporated into the PMA, or any PMA supplement related to submission. The PMA file may not be disclosed by the FDA before an approval order unless it previously has been publicly disclosed or acknowledged. After PMA decision, the following information are immediately available for public disclosure including safety and effectiveness data and protocol for a test or study unless the protocol is shown to constitute trade secret or confidential commercial or financial information, adverse reaction report, product experience report, consumer complaints, and all the correspondence and written summaries of oral discussions relating to PMA file. The FDA shall abandon PMA if the applicant fails to respond to a request for additional information within 180 days after the date FDA issues the request, or if all legal appeals after the denial of PMA have been exhausted, if PMA has been voluntarily withdrawn, if the device has been reclassified, or if the device is found to be equivalent to class I or class II device.

(a) Research conducted outside the United States: A PMA based solely on foreign clinical data may be approved if the data are applicable to US population and US medical practice and if the studies have been performed by clinical investigators of recognized competence. Applicants shall meet the FDA officials in a "presubmission" meeting when approval based solely on foreign data is sought.
(b) Service of orders: The orders issued will be served in person by a designated officer or employee of FDA on, or by registered mail to, the applicant or the designated agent at the applicant's or designated agent's last known address in FDA's records.
(c) Product development protocol (PDP): A class III device for which a product development protocol has been declared completed by FDA under this chapter will be considered to have an approved PMA.

A. *Premarket Approval Application (PMA)*

A. Application

The PMA shall be signed by the applicant residing within the United States or shall be countersigned by an authorized representative residing or maintaining a place of business in the United States. The PMA application shall include the name and address of the applicant, separate sections on nonclinical laboratory studies and on clinical investigations involving human subjects. The trade secret or confidential

commercial or financial information is provided but identified to be a confidential information.

(a) Summary: Details of summary shall include indications of use of the device to diagnose, treat, prevent, cure, or mitigate including a description of target patient population. The device is described in detail, functionally, physically, along with the manufacturing process and performance characteristics of the device. The generic name and the proprietary name or trade name of the device shall also be included. It should also describe the alternative practices or procedures for diagnosing, treating, preventing, curing, or mitigating the disease or condition. Summary of studies shall include description of objective of the study; description of experimental design of study; brief description of data collection; analysis results whether positive, negative, or inconclusive; nonclinical laboratory studies; clinical investigations involving human subjects submitted in the application along with the conclusion; and valid scientific evidence drawn from the study.
(b) Description of device shall include pictorial representations; functional components or ingredients of the device; properties of the device relevant to the diagnosis, treatment, prevention, cure, or mitigation of a disease or condition; principles behind operation of the device; and methods used for manufacture, processing, packing, storage, installation, and quality control.
(c) FDA shall determine whether to approve or deny approval of the application based on nonclinical and clinical laboratory studies. The results of nonclinical laboratory studies include microbiological, toxicological, immunological, biocompatibility, stress, wear, shelf life, and other laboratory or animal tests as appropriate. The results of clinical investigations involve human subjects with clinical protocols, number of investigators, subjects per investigator, subject inclusion and exclusion criteria, study population, study period, safety and effectiveness data, adverse reactions and complications, patient discontinuation, complaints, device failures, replacements, tabulations of data from all individual subject report forms including of those who died during clinical investigation or who did not complete the investigation, results of statistical analyses of the clinical investigations, device failures and replacements, and contraindications and precautions for use of the device.

B. PMA Amendments and Resubmitted PMAs

An applicant may amend a pending PMA or supplement to revise the existing information or to provide additional supporting information. FDA also may request the applicant to amend a PMA to provide necessary information to complete the review. Such PMA amendment shall include the original submission details along with reason for submitting the amendment, and FDA may extend the time required for its review up to 180 days, and if not received, it shall consider pending PMA or PMA supplement to be withdrawn voluntarily by the applicant.

C. PMA Supplements

PMA supplement shall be submitted after FDA's approval of a PMA for making a change affecting the safety or effectiveness of the device. A supplement is required if there are new indications for use of the device; labeling changes; use of a different facility or establishment to manufacture, process, or package the device; and changes in sterilization procedures packaging, performance, specifications, circuits, components, ingredients, principle of operation, or layout. FDA will identify the information that needs to be included in the report or the supplement, and if change is required, it shall be made 30 days after FDA files the PMA supplement unless FDA requires the PMA holder to provide additional information or disapproves a supplement.

B. *FDA Action on a PMA*

(a) Time frames for reviewing a PMA

FDA will review the PMA within 180 days after receipt of an application and send an approval order, an approvable letter, a not approvable letter, or a denying approval. An applicant has the opportunity to amend or withdraw the application after receiving approvable letter and the not approvable letter.

(b) Filing a PMA

Within a time period of 45 days, FDA will notify the applicant, in writing, whether the PMA has been filed. The notice will include the PMA reference number and date filed. From the date of filing, the 180-day time period for review of a PMA starts. The filing of an application itself denotes a threshold determination about the completion of PMA to permit a substantive review. If FDA refuses to file, it will notify with reasons for refusal after which the applicant can resubmit the PMA with the necessary additional information. Upon request after resubmission, FDA shall hold an informal conference within 10 working days and will produce its decision of filing within 5 working days. If FDA does not reverse its decision, the applicant may request reconsideration to the directors of appropriate agency as applicable, and it shall be considered as a final administrative action. The refusal of a PMA is considered if the application is incomplete, has missing information or omission of any item, contains false statement of material fact, or is not accompanied by a statement of certification or disclosure.

(c) Procedures for Review of a PMA

FDA refers the PMA to each member of its own panel for review and communicates mediating the applicant and the panel to respond to additional information or questions raised during the review. The advisory committee shall hold a public meeting or a telephone conference and submit a report to FDA which will have recommendations and the basis for the same signed by the chairperson of the committee. This happens within the later of 180 days from the date of filing of the PMA. FDA will issue the approval of a PMA if there are no reasons for denying it and give the public notice of the order, including notice for any interested concerns to request review. FDA's homepage displays the notice of approval with a brief

summary of information regarding safety and effectiveness of the device, basis of approval, and adverse effects if any. The applicant shall receive an approvable letter if they need a specific additional information or conditions to be agreed by the applicant or a not approvable letter if it describes the deficiencies in application for one or more reasons. In response to an approvable or not approvable letter, the applicant may amend the PMA, file a petition in form for reconsideration, or withdraw the application. FDA will consider a PMA to have been withdrawn voluntarily if the applicant fails to submit a written request for an amendment needed within 180 days after FDA issues a request or if the applicant fails to respond in writing to an approvable or not approvable letter within the same time period or a written notice of withdrawal is submitted by the applicant.

(d) Denial of Approval of a PMA

FDA shall deny an approval if the applicant fails to meet the requirements in the application including various reasons: false statement of facts or labeling of the device without complying the requirements. FDA, if denied permission to inspect at a reasonable time or manner at the facilities, controls, or to access to verify any records pertinent to the application, shall propose denial of approval. Similar decision shall be recommended if conditions prescribed were not conducted in compliance with good laboratory practice regulations, or do not support the validity of the study. FDA shall deny approval for all the clinical investigations involving human subjects, if not accompanied by the institutional review board or informed consent regulations, or found in line with rights or safety of human subjects. The public notice of an order denying approval of the PMA will be placed on FDA's homepage with detailed summary of the reasons.

(e) Withdrawal of Approval of a PMA

An approval of a PMA shall be withdrawn if FDA determines that post-approval requirement has not met the regulations proposed or if the nonclinical/clinical laboratory investigations are found in compliance with the good laboratory practice regulations or adequately protected for maintaining the rights or safety of human subjects. FDA will decide to withdraw approval of a PMA after seeking advice of an advisory committee and after giving a notice of opportunity to the applicant for an informal hearing if requested. If still found unsatisfactory, FDA shall give the public notice of an order withdrawing approval of a PMA with appropriate explanation.

(f) Temporary Suspension of Approval of a PMA

FDA, if suspects the probability that a device would cause serious, adverse health consequences, or death, shall issue an order temporarily suspending approval of a PMA. If FDA issues such an order, within 60 days, the agency holds a hearing on whether a permanently withdraw an approval of PMA.

C. *Post-approval Requirements*

(a) General

After the PMA approval of a device, it is mandatory to manufacture, pack, store, label, distribute, or advertise as specified in the PMA application; hence post-approval requirements are important to follow.

(b) Post-approval Requirements

Post-approval requirements may include many clauses as conditions to approval of the device like the following: restrictions of sale; distribution of use of device on particular conditions; continuing evaluation and periodic reporting on safety, effectiveness, and reliability of the device; prominent display in the labeling of a device and in the advertising of any restricted device of warnings, hazards, or precautions regarding the device's safe and effective use, including patient information; inclusion of identification codes on the device or its labeling on cards to be inserted for patients; providing the identity of any patient be disclosed in records maintained to verify a record or a report; submission of periodic reports as specified during the application; batch testing of the device; and providing the records and reports required to inspect at a reasonable time or manner at the sites of producing/storing/shipping the device.

(c) Reports

The holder of an approved PMA shall comply with all the requirements as mentioned in the order of device approval. The periodic reports shall submit the changes if available along with summary and bibliography of unpublished reports of data from any clinical investigations or nonclinical laboratory studies involving the device or related devices.

D. *Humanitarian Use Devices*

(a) Purpose and Scope

The discovery of devices intended to benefit patients in treatment or diagnosis of diseases or conditions that affect or are manifested in not more than 8000 persons in the United States per year is encouraged under HUD designation of a medical device. Obtaining marketing approval for a HUD involves obtaining designation of the device from FDA's Office of Orphan Products Development and submitting an HDE application to respective center as applicable.

(b) Designation and HUD Status

(i) Request for designation: The process starts with submitting a request to FDA's Office of Orphan Products Development which shall contain name and address and contact details of the applicant;

a statement of reason for HUD designation for a rare disease or condition or a valid subset of a disease or condition which shall be identified with specificity; proposed indications for use of the device, reasons why such therapy is needed; scientific rationale for the use of the device; and documentation with appended references to demonstrate the disease or condition and its relation to the people in the United States.

(ii) FDA action: FDA will take one of the following actions on request for HUD designation in 45 days: Approve the request and notify the applicant or return the application for further review or disapprove the request.
(iii) Revocation of designation: If the request for designation contained false statements/facts/omitted material information or if the device is not eligible for HUD designation based on evidences provided, FDA shall revoke a HUD designation.

(c) Original Applications

The applicant or an authorized representative shall sign the HDE; if he does not reside in the United States, it shall be countersigned by an authorized representative in this country. The application shall include a copy of reference to the determination of qualification of the device as a HUD made by FDA's Office of Orphan Products Development, explanation of why the benefit of health in the device usage outweighs the risk of injury or illness, summary of all clinical experience or investigations, and labeling requirements. If the price of the device is more than $250, a report made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants is provided.

(d) HDE Amendments and Resubmitted HDEs

An HDE or HDE supplement may be amended or resubmitted by the applicant itself or provided at the request of the FDA as similar to PMA but without the timeframes. If a written response is not received within 75 days of date of the request, the pending HDE or HDE supplement is proposed for voluntary withdrawal by the applicant.

(e) Supplemental Applications

Once the original application of HDE is approved by the FDA, an applicant must submit supplements as similar to PMA's as per HUD requirements.

(f) New Indications for Use

An applicant seeking a new indication for use of a HUD shall obtain a new designation of HUD status and submit an original HDE as explained earlier.

(g) Filing an HDE

The filing of an HDE means that FDA has found that the application is sufficiently complete to subject it for further review. Within 30 days, FDA shall notify the applicant about the filing review result.

(h) Timeframes for Reviewing an HDE

Within 75 days after a filing of an HDE, for which there is no major amendment pending, FDA shall send the applicant an approval order, an approvable letter, a not approvable letter, or an order denying approval.

(i) Procedures for Review for an HDE

FDA shall begin a substantive review of an HDE after filing by constituting a panel for reviewing process, and this advisory committee shall recommend and report within 75 days from the date of filing of an HDE. An approval order is given if none of the reasons for denying is pointed after review except for minor deficiencies in final draft labeling. The notice of approval will be published in the Federal Register. An approvable letter will be sent if the agency believes that it can approve if specific additional information is submitted or specific conditions are agreed by the applicant. A not approvable letter is provided if the application may not be approved for one or more reasons due to deficiencies in the application and opportunity is given for submitting an amendment within 75 days.

(j) Denial of Approval or Withdrawal of Approval of an HDE

FDA may deny the approval or withdraw approval of an application, if the application fails to meet the requirements of an HDU or any condition of approval imposed by an IRB or by the FDA. Denial of approval suggests the following:

(i) Lack of showing a reasonable assurance that the device is safe as prescribed, recommended, or suggested in the labeling
(ii) Lack of reasonable basis to conclude the probable benefit to health which should outweigh the risk of injury or illness
(iii) Evidence of untrue statement of material fact, or omission of information
(iv) Clinical or nonclinical laboratory studies not conducted in compliance with the good laboratory practice or informed consent regulations

(k) Temporary Suspension of Approval of an HDE

An HDE or HDE supplement may be temporarily suspended for the same reasons and the same manner.

(l) Confidentiality of Data and Information

The HDE file includes all the data and information submitted with or referenced in the HDE including amendments, supplement related to submission. Any record in the HDE file will be available for public disclosure in accordance with the FDA's norms. The disclosure by FDA shall subject to the same rule like that of a PMA.

(m) Institutional Review Board Requirements

Once a HUD is approved, the HDE holder is responsible for attending to requirements of the Institutional Review Board (IRB). A HUD shall be administered only if the use of device is approved by an IRB; however, in an emergency situation, to prevent serious harm or death of a patient, a HUD may be administered without prior approval by an IRB, where the physician shall provide a written notification within 5 days after the use to the chairman of the IRB with the explanation with the details of the patient involved and date of usage and the reason for its use. A HUD holder shall notify FDA of any withdrawal of approval for use of HUD by reviewing IRB within 5 working days after being notified of the withdrawal of approval.

(n) Post-approval Requirements and Reports

All the HUD approved devices shall be subjected to post-approval requirements and reports in a complete, accurate, and timely manner. The periodic reports shall include an update of information regarding the device, number of devices shipped or sold since initial marketing approval, number of devices used per patient, or if a single device is used for multiple patients. This shall include information describing clinical experience, safety instructions, statement of contraindications, warnings, precautions, and adverse reactions in the device's labeling. In addition to it, an HDE holder shall maintain records of the names and addresses of the facilities to which the HUD has been shipped, and such records shall be maintained in accordance with the HDE approval order.

2.11 Part 820: Quality System Regulation [18]

Quality system regulation is in line with current good manufacturing practice (CGMP), and these govern the methods, facilities, controls used in design, manufacture, packaging, labeling, storage, and servicing of any finished device intended for human use. This system shall ensure that the device will be safe and effective in compliance with the FDA and Cosmetic Act. This part shall inform the basic requirements applicable to manufacturers of the finished device manufactured, imported, and offered in the United States, and this system also is applied to the manufacturer from a foreign country. Anyone who wishes to apply for an exemption or variance from any device quality system requirement has to request to the FDA, and the agency may initiate and grant the variance in the best interest of the public health.

For any device, its manufacturers shall develop and maintain a unique quality system that is specific for the device and ensure that it meets the requirement as per the quality system regulations as follows:

(a) *Management responsibility:* The management with executive responsibility is responsible for the development of its policy with "quality" as the main component. The same management shall ensure that the quality policy is made available, implemented, and maintained at all levels. The manufacturer shall be responsible for all the personnel who manage, perform, and assess work quality through proper training, and they will provide adequate resources for quality performance including internal quality audits. These shall be managed by a representative who shall be appointed from the members of the management to ensure the requirements of the quality system regulations. He/she will head the review of suitability and effectiveness of the system at defined intervals and with sufficient frequency, and these dates and results are to be documented. A quality planning and framework of quality system procedures form the initial outline of this part.
(b) *Quality audit*: The manufacturer of the device shall start the process by developing procedures for the quality audits whereby it is assured that the system is

in compliance with the quality system requirements. These audits shall be conducted by individuals who are not in direct responsibility for the matters being audited. A report of the audits and the re-audits (if conducted) shall be made and reviewed by the management.

(c) *Personnel*: The manufacturer shall ensure the availability of adequate personnel with qualified education, background, training, and experience to assure the activity of quality system regulations. The training of all the personnel shall be conducted to make them aware of all the device defects or errors that may be encountered during the improper performance.

(d) *Design controls*: Each manufacturer shall establish and maintain procedures to control the design of the device of any class (class I–III). The design and development is planned with different groups which shall be reviewed, updated, and approved as it evolves. The basis of the design input is to ensure that it's appropriate for the intended use and needs of the user or the patient. These input requirements shall be documented and reviewed and approved by appointed designated individuals, which shall be documented with date and signature. Based on this input requirements of the device designed, device output procedures shall contain and make reference to acceptance criteria which are essential for the proper functioning of the device of interest, and again this device output shall be documented, reviewed, and approved before release. These designs produced are reviewed by an individual who is not in direct responsibility for the design state, and the results shall be documented in the design history file (DHF). Each manufacturer shall also develop and maintain procedures for validation of the device design. This validation shall include software validation and risk analysis (if appropriate) and is documented in the DHF file with date and method. Hence each manufacturer shall establish and maintain a DHF for each type of device, and each DHF shall contain all the records necessary to demonstrate that the design was developed in accordance with the approved design plan.

(e) *Document controls*: Each manufacturer shall develop and maintain procedures to control all the documents established to meet the requirements of the quality system regulations. The approvals including the date and signature shall be documented, and all the changes in the documents shall be reviewed and approved by the individuals in the organization in a timely manner. The change records shall include the description of change, identification of affected documents, signature of the individual, the approval date, and the effect date.

(f) *Purchasing controls*: Each manufacturer shall establish and maintain procedures to ensure that all the purchased or received the products are in line with specific requirements. This involves evaluation and documentation of potential suppliers, contractors, or consultants. The producing documents shall include an agreement that the suppliers and contractors agree to notify the manufacturer in case of any change in the product or service that may affect the quality of the finished the device.

(g) *Identification and traceability*: Each manufacturer shall establish and maintain the procedures for identification and traceability of each product during each

stage including the receipt, production, distribution, and installation. This is important for the devices used to support or sustain life like surgical implants. These procedures shall facilitate corrective actions.

A. *Production and Process Controls*

This part includes the documented instructions or standard operating procedures (SOPs) and methods to define and control the production system, the monitoring and control process parameters, and the approval of these parameters. Any change from the specification shall be verified and approved and validated, and these will be documented in accordance with the quality system regulations. For some of the devices, the production will be affected by the different environment conditions, and hence the environmental control systems shall be in place, and it is periodically inspected and documented. Each personnel involved in the manufacturing shall maintain the requirements of health, cleanliness, and personal protective practices which can affect the product quality adversely. Adequate training of these personnel is given through our trained professional before involving them into the process. Steps to prevent any contamination of the equipment should be available in the buildings of production and storage. The buildings and equipment used in the manufacturing process shall meet the design to facilitate the specific requirements, and a maintenance schedule should be available; the details of inspection and adjustments made during inspections shall be documented. The source material used for the manufacturing should be of good quality, and the details of it shall be documented in DHF. Even though automated data processing system is used for production, the manufacturer shall validate the software before approval and shall be documented.

(a) *Inspection, measuring, and test equipment*: Each equipment used in the process shall be tested by mechanical, automated, or electronic inspection methods, and it is routinely calibrated, inspected, checked, maintained, and documented. The calibration procedures of each equipment shall check the accuracy and precision in accordance with national or international calibration standards. The equipment identification, calibration dates, and the next calibration date shall be documented on the equipment.
(b) *Process validation*: Each manufacturer shall ensure that the validation processes is performed by qualified individuals. The monitoring and controlling methods and the date performed shall be documented. If changes or deviations are observed, the revalidation can be conducted if appropriate.

B. *Acceptance Activities*

(a) *Receiving, In-process, and Finished device acceptance*: Each incoming product shall be inspected and tested before acceptance or rejection. Documentation of finished device acceptance ensures each production run and batch or number of devices as per the design criteria. Hence, finished devices shall be held until all

the data, documentation, and authorization are completed. The records shall include the acceptance activity, dates, results, and signatures in the DHR.

(b) *Acceptance Status*: The acceptance identification shall be maintained throughout manufacturing, packaging, labeling, and installation of each product produced.

C. *Nonconforming Product*: If a product doesn't conform to the specified requirements, details procedures to address the identification, documentation, evaluation, segregation, and disposal shall be followed and documented. This shall be followed by rework, retesting, and reevaluation of the products as per current approved specifications.

D. *Corrective and Preventive Action*: Appropriate corrective and preventive actions shall be in place for analysis of the process, work operations, concessions, quality audit reports, complaints, and returned product, and all other quality problems and appropriate statistics shall be employed to detect the recurring quality problems. The corrective and preventive actions are validated to ensure that the action is effective and does not affect the finished device in any manner. These relevant information on identified quality problems are submitted for the review of the management.

E. *Labeling and Packaging Control*

(a) *Device labeling*: Labels of the device shall be printed and displayed legibly and with appropriate details about processing, storage, handling, and distribution. Labels are released after inspection for the accurate details, including the unique device identifier (UDI) or universal product code (UPC), expiry details, control number, storage instructions, and other processing instructions. Labels are designed for proper identification and to prevent mix-ups.

(b) *Device packaging*: The material used for packaging the device and the shipping containers are designed and developed for protection of the device of interest from any alteration or damage from the time of production till distribution.

F. *Handling, Storage, Distribution, and Installation*

The handling of device is critical, and issues like mix-ups, damage, deterioration, and contamination can occur during handling and should be managed appropriately. Any product or device deteriorates over a fixed time duration, and hence it shall be stored to facilitate the safe and proper condition before distribution. The stock sheets with details of storage areas and stock rooms are maintained with the manufacturer. Before the distribution, the purchase orders are approved and checked to ensure the errors are resolved if any before the devices are released for distribution, and those devices which have deteriorated beyond acceptable fitness are not distributed. The distribution details include the location planned, name and address of initial consignee, quantity of devices shipped, date, and numbers of contact for the distribution. Once distributed, the manufacturer shall establish and maintain installation and appropriate test procedures and demonstrate the device to the end user or the patient.

G. *Records*

(a) *General requirements*: All records are maintained by the manufacturer and provided accessible to the responsible officials or FDA for in-depth inspections. Therefore, the records are maintained legibly and stored from any damage and also backed up in automated data processing systems. These records are maintained in confidential and are disclosed only when specified by the producers and the agency.
(b) *Device master record*: The device master records (DMRs) shall be available with the manufacturer which shall contain device specifications including drawings, composition, formulation, and component and software specifications; production specifications including methods, procedures, and environment specifications; quality assurance procedures like acceptance criteria and equipment used for audits; *and* packaging and labelling specifications and installation and servicing methods.
(c) *Device history record*: The device history records (DHRs) shall contain the batch, lot, or unit, dates of manufacture, and quantity manufactured and distributed. It shall also contain the primary identification label, unique device identifier (UDI), or universal product code (UPC) specific for the device.
(d) *Quality system record*: The quality system record (QSR) shall include location of documents and procedures following for assuring the quality of the device which shall be in accordance with the quality system regulations.
(e) *Complaint files*: Complaint files shall contain all documents pertaining to receipt, review, and evaluation of the complaints. The procedures shall ensure that all the complaints shall be processed in a uniform and timely manner and documented upon receipts including oral complaints if any. In case of unattended complaints, the reason for the same and details of the individual responsible for decision shall be noted. Once a complaint is registered, the date of complaint, unique device identifier (UDI), or universal product code (UPC) shall be recorded, including the nature and details of complaint, date of results of the investigation, any corrective action taken, and any reply to the complainant.

H. *Servicing*: In case the device supplied needs servicing, the manufacturer shall establish and maintain the instructions and procedures for performing and verifying it as per specified requirements. All the service reports shall be analyzed and documented with the name of device, UDI, or UPC, control numbers, date of service, service personnel details, and method of testing used.
I. *Statistical techniques*: The manufacturer shall develop procedures for identifying valid statistical techniques required for establishing, controlling, and validating the processes and device characteristics. Sampling plan can be made based on a valid statistical understanding, and these shall be documented.

2.12 Part 821: Medical Device Tracking Requirements [19]

A. *General Provisions*

(a) *Scope*: As per the Federal Food, Drug, and Cosmetic Act of the FDA, the manufacturer shall adopt a method of tracking a class II or III device, if failure of the device would be reasonably likely to have serious adverse health consequences, or intended to be implanted in the human body for more than a year, or if the device is a life-sustaining one, it is referred to as a "tracking device." In case of a tracking device, it can be traced from the manufacturing facility through the distributor networks including distributors, retailers, rental firms, and other commercial enterprises and device user facilities. The tracking system is the responsibility of the manufacturer, and any person who permanently closes the business of the device shall notify the FDA and provide the complete set of its tracking records and information. In that case, the other person who acquires the right to manufacture or distribute the tracking devices will be responsible for continuing the tracking responsibility.
(b) *Exemptions and variances*: A manufacturer or a distributor shall request exemption or variance from medical device tracking responsibility by providing a petition containing the name of device, class type, reasons and justification explaining why tracking is unnecessary, and alternate steps if available. This petition shall be approved by the Director, Office of Compliance, CDRH, before deemed effective.
(c) *Imported devices*: In case of a device manufactured in a foreign country, the importer of the tracked device in the United States shall be considered as the manufacturer and shall comply to all requirements as applicable.

B. *Tracking Requirements*

(a) *Devices subject to tracking*: A manufacturer of any class II or III device must track that device in accordance with FDA requirements if the agency notifies the need for tracking during the premarket notification submissions and premarket approval applications.
(b) *Devices tracking system and content requirements*: The manufacturer shall adopt a method of tracking as per each type of device. Upon FDA's request, the UDI, lot number, batch number, model number of the device, date of shipment, contact details of the patient, location of the device, and name and details of the treating physician who recommended the device are provided within 10 days of request. A standard operating procedure of device tracking shall be established and shared to the FDA upon request. This SOP shall include the data collection and recording procedures, methods for recording all modifications, or changes to the tracking system if any. A quality assurance program which includes audit procedures with statistical relevant sampling to ensure the accuracy of data and functioning of tracking system shall be established.

C. *Additional Requirements and Responsibilities*

(a) *Tracking obligations for persons other than device manufacturers*: Apart from the manufacturers of the device, upon purchasing or acquiring any interest of the same, the distributor(s) are obliged to provide the following details: name and address of the distributor (final/multiple distributors), UDI, lot number, batch number, model number or serial number of the device, date of receipt, end user, and return date or permanent disposal date (if appropriate). The distributor(s) shall maintain all records to be made available for the manufacturer during audits.

D. *Records and Inspections*

(a) *Availability*: Manufacturers or distributor(s) shall make a document of each information collected and maintained from all the records and related events and persons identified. This shall be provided to the FDA personnel upon issuance.
(b) *Confidentiality*: Any patient receiving a device shall be subjected to tracking requirements but however may refuse to release or refuse permission to release the patient's name, address, telephone number, social security number, or other information for the tracking purpose. FDA shall protect the records and other information submitted and shall not be available for public disclosure. However, patient names and other identifiers shall be disclosed to the manufacturer or to treating physician to pursue the health aspects of the patient.
(c) *Retention of records*: The manufacturer or the distributor shall maintain records about useful life (time when the product is in use) of the tracked device. These records shall be retired only when the device is no longer used, explanted, or returned, or when the patient using it is no more existing.

2.13 Part 822: Postmarket Surveillance [20]

Postmarket surveillance as per section 522 of the Federal Food, Drug, and Cosmetic Act is required for all class II and III devices which upon failure would result in serious adverse health consequences or are implanted in the human body for more than 1 year or used to sustain life of the user. The purpose of postmarket surveillance is to collect useful data which can reveal unforeseen and anticipated adverse events or any information that protects the public health aspect of the device usage.

A. *Notification*: The FDA shall send a letter called "postmarket surveillance order" which notifies the requirement to conduct the postmarket surveillance. Before issuing this order, FDA requests the manufacturer to submit information about the device to specify the subject of the surveillance order and reason for the requirement of the surveillance. Once considered necessary, the FDA shall notify the postmarket surveillance based on the surveillance question. In case the manufacturer decides not to conduct the postmarket surveillance, a request shall be submitted with the Director, Office of Surveillance and Biometrics,

seeking internal review of the order and requesting an informal hearing or review by the Medical Devices Dispute Resolution Panel of the Medical Devices Advisory Committee.

B. *Postmarket surveillance plan*: Once the postmarket surveillance order is received, the manufacturer shall submit the plan to conduct the same within 30 days to the respective agency in-charge. Upon receiving the plan, the agency shall send an acknowledgement letter with unique document number assigned for any further correspondence. The initial details to be included in the submission are the following: organizational information, name, address, generic/trade names, address of contact person, premarket application/submission, description of device, product codes, and indications for use. The postmarket surveillance plan shall include the following: the objective addressing the question put forth in the FDA order, study subject details, clinical parameters/outcomes, methodology of surveillance, sample size and units of observation, sources of data, data collection plans and forms, consent document (if applicable), Institutional Review Board information, patient follow-up plan, procedures for monitoring conduct and progress of the surveillance, estimate of duration of surveillance, data analyses, and statistical tests planned. The duration allowed for postmarket surveillance shall be mentioned in the order usually for a period of up to 36 months, longer if needed. If the prospective period is not agreeable between the manufacturer and the FDA, the matter shall be resolved through Medical Devices Dispute Resolution Panel.

C. *FDA review and action*: FDA shall review the submission if it's received complete as per the requirements, and after which a designated person with essential qualifications and experience shall be assigned to conduct the surveillance. The review shall be completed within 60 days of receipt, and decision or identification of actions needed shall be notified. FDA shall send an approval order/approvable letter/disapproval letter. If the manufacturer fails to submit a revised or new plan after the review, the device shall be misbranded, and these devices can be seized. The personnel involved shall pay civil money penalties or prosecuted. If changes required in the plan are suggested, resubmission shall be proceeded; however, the changes should not affect the nature or validity of the data collected in the initial device approval order. If the manufacturer disagrees to the review of the FDA, they shall request a meeting with the authority responsible for the postmarket surveillance, seeking internal review and informal hearing through Medical Devices Dispute Resolution Panel. The content of the postmarket surveillance plan submission shall be maintained confidential until approved; however, the trade secret and commercial information (if any) shall be protected.

D. *Responsibilities of manufacturers*: Once notified about the requirement to conduct postmarket surveillance, the manufacturer shall submit the plan within 30 days. The manufacturer shall ensure that the surveillance is initiated and conducted diligently, until the submission of reports, required in a timely manner. In case of any change in the ownership of the device's company, it shall be notified, and the new owner shall be obliged to conduct the surveillance. Similarly,

if manufacturers decide to close the business or stop marketing of the device of interest, it shall be notified, and plans to complete the postmarket surveillance or terminate it should be discussed.

E. *Waivers and exemptions*: The manufacturer shall request to waive any specific requirement under postmarket surveillance with supporting document with explanation of why it is believed an exempt is applicable for the device, and this shall be submitted separately or with the postmarket surveillance submission document.

Records and Reports The manufacturer shall maintain copies of all correspondence with the investigating team or FDA including reports, signed agreements, plan, approval order, data collected and analyzed for conducting the postmarket surveillance plan, or any other records involved during the postmarket surveillance. Similarly, the investigators shall keep all the correspondence between them, the FDA, and the manufacturer and the plans approved for conducting the surveillance. All these records are preserved for a period of 2 years after acceptance of final report. In case of any change in plan, FDA shall be notified within 10 working days; otherwise once initiated, the program is regularly inspected by authorized FDA employees in the facility where the device is held. FDA shall be permitted at a reasonable time and manner to inspect the copy of any records related to this surveillance, or it shall be provided upon request within 72 hours of initiation of the inspection. The records of the individual subjects shall be inspected if the reports are found incomplete, inaccurate, false, or misleading. The manufacturer shall submit interim and final reports as per the postmarket surveillance plan and additional information if found necessary.

2.14 Part 830: Unique Device Identification [21]

A unique device identifier (UDI) means an identifier that adequately identifies a device through its distribution and use. An UDI is composed:

(a) Device identifier, a mandatory, fixed portion of UDI that identifies the specific model or version of the device and the device label
(b) Production identifier, a conditional, variable portion of UDI that might include the lot or batch of manufacture, serial number of specific device, expiration date, and specific date of device manufactured

It is required that the UDI must:

(a) Be issued under a system operated by the FDA or an FDA-accredited issuing agency
(b) Conform to the following international standards:

(i) ISO/IEC 15459-2:2006, Information technology-Unique identifiers-Part 2: Registration procedures
(ii) ISO/IEC 15459-4:2008, Information technology-Unique identifiers-Part 4: Individual items
(iii) ISO/IEC 15459-6:2007, Information technology-Unique identifiers-Part 6: Unique identifier for product groupings

(c) Only use characters and numbers from the invariant character set of ISO/IEC 646:1991, Information technology-ISO 7-bit coded character set for information interchange

Only one device identifier from any particular system for issuance of UDI shall be used to identify only one particular version or model of a device. When a change is made to the device, a new UDI must be assigned to distinguish the new version or model device from its previous one. In case the model or version of the device is discontinued, its UDI will not be reassigned to another device. On re-introducing the discontinued version or model of the device with no change, then the same UDI can be used. For relabeling a device, a new device identifier can be assigned to the device, but its relationship with previous device identifier should be kept in record.

Responsibilities of FDA-Accredited Issuing Agency
A private organization is eligible to apply for FDA accreditation, or FDA by itself can act as an issuing agency. For initial accreditation, the applicant shall notify their desire to be accredited by sending a notification by email or by correspondence to the FDA. If approved, the initial term of accreditation for an issuing agency shall be for 3 years and can be periodically renewed for 7 years. To maintain its accreditation as an issuing agency, they must operate:

(a) To meet the requirements of UDI to adequately identify a device through its distribution and use.
(b) Conform to international standards: ISO/IEC 15459-2, ISO/IEC 15459-4, ISO/IEC 15459-6.
(c) Only use characters and numbers from the invariant character set of ISO/IEC 646.
(d) With single set of consistent, fair, and reasonable terms and conditions to all users.
(e) To protect against conflicts of interest between the issuing agency (and its officers, employees, and other agents) and labelers (and its officers, employees, and other agents).
(f) Make available information concerning its system for UDI assignments.
(g) List of labelers using their system for UDI assignment should be maintained, and an electronic copy of the same must be submitted to FDA upon request anytime or at end of each year.

Suspension or Revocation of FDA Accreditation as an Issuing Agency
Accreditation of an issuing agency can be suspended or revoked by the FDA with a notice and opportunity for informal hearing, if FDA finds an issuing agency or any officer, employee, or other agent of the issuing agency:

(a) Is guilty of misinterpretation or failed to disclose potential information during accreditation
(b) Failed to fulfill the responsibilities as an issuing agency
(c) Failed to protect against conflict of interest
(d) Engaged in any anticompetitive activity to restrain trade
(e) Violating or aided and abetted in violation of any regulation under section 510(e) or 519(f) of the FDA Act

2.15 Part 860: Medical Device Classification Procedures [22]

This part of the regulation sets forth the criteria and procedures in accordance with Sections 513, 514(b), 515(b), and 520(l) of the FDA Act, used for classification and determination of class of regulatory control (class I, class II, and class III) appropriate to provide assurance for the safety and effectiveness of the medical devices. Three categories of regulatory control for medical devices are:

(a) Class I (general controls): This class of device is subjected to only general control authorized by or under Sections 501 (adulteration), 502 (misbranding), 510 (registration), 516 (banned devices), 518 (notification and other remedies), 519 (records and reports), and 520 (general provisions) of the Act. The general controls are adequate to assure the safety and effectiveness of these class I device.
(b) Class II (special controls): This class of device will be or will eventually be subjected to special controls. The general controls alone are inadequate for safety and effectiveness assurance in class II devices; therefore, special controls including promulgation of performance standards, postmarket surveillance, patient registries, guidance on premarket notification submission (in accordance with section 510(k) of the FDA Act), and other appropriate recommendations are required for such assurance.
(c) Class III (premarket approval): This class of device will require premarket approval in accordance with Section 515 of the FDA Act. A device is in class III if general controls provide insufficient information for safety and effectiveness assurance or if a need for special control is required or if the device is life-supporting or life-sustaining or if the device presents a potential unreasonable risk of illness or injury.

Determination of Safety and Effectiveness
The Commissioner of the FDA refers the device to the appropriate classification panel, which is one of the advisory committees established by the Commissioner under Section 513 of the FDA Act for making recommendations on the classification and reclassification of devices. The recommendation will include:

(a) Summary of reasons for the recommendation
(b) Summary of data upon which the recommendation is based
(c) Report on the health risks (if any) presented by the device

Manufacturers may submit evidence to FDA to substantiate the safety and effectiveness of device; however, the FDA relies only on the valid scientific evidence generated from well-controlled investigations, partially controlled studies, and objective trials conducted by qualified experts. Based on the scientific evidence using laboratory animals, clinical studies on human subjects, and analytical studies, FDA ensures the absence of unreasonable risk of illness or injury associated with intended uses and usage conditions of the device. A device is considered safe and effective when its intended use of the device, adequate directions for use, and warnings against unsafe use are proven in a significant portion of target population by clinically significant results. The classification panel reviews the evidence concerning safety and effectiveness and prepares advice to the commissioner, and the commissioner will apply rules for determining safety and effectiveness of a device. The panel recommendation is regarded preliminary until the Commissioner reviews and publishes it in the FEDERAL REGISTER, together with the proposed regulation for device classification for comments. The Commissioner reviews the comments and issues the final regulation for classifying the device and other devices of that generic type.

Exemptions from Sections 510, 519, and 520(f) of the FDA Act

In case of recommendation for a medical device to be classified as class I, recommendations on the exemption of one or more requirements of the following sections of the FDA Act can be made: Section 510 (registration, product listing, and premarket notification), section 519 (records and reports), and section 520(f) (good manufacturing practice requirements of the quality system regulation). In the case of a recommendation for classification of a medical device into class II, whether the device should be exempted from the premarket notification requirement under section 510, will be decided in accordance with §860.15. For the purposes of classification, establishment of special controls for class II devices, and premarket approval of class III devices, the Commissioner and the classification panels consider the following factors:

(a) The person for whose use the device is represented or intended
(b) Conditions of use including prescribed or recommended or advertised or suggested in the labelling for the device
(c) Health benefits from device usage outweigh the probable injury or illness as a result of such use
(d) Reliability of the device

Reclassification

Under Sections 513(e) and (f), 514(b), 515(b), and 520(l) of the FDA Act, an interested person or manufacturer or importer may submit a petition for reclassification of a device. Unless provided in writing by the commissioner, any petition for reclassification of the device shall include:

(a) Specification for the type of device requested for reclassification
(b) A statement on action requested, such as “It is requested that….. device(s) be reclassified from class III to class II”

(c) A statement on the basis of disagreement with the present device classification
(d) A full statement of reasons supported the reclassification and how the proposed classification assures the safety and effectiveness of the device
(e) Relevant data and new information with source documents relevant to the petition

Within 180 days after the filing of a petition for reclassification under this section, the Commissioner will either deny the petition by order published in the Federal Register or give notice of the intent to initiate a change in the classification of the device. The Commissioner may initiate the reclassification of the device, by either referring a reclassification petition to the panel under §860.134(b) or consulting with panel regarding the petition under §860.130(d) or received in a proceeding under §860.133(b), or the Commissioner chooses to consult with a panel with regard to the reclassification of a device initiated by the Commissioner under §860.134(c) or §860.136. If a device is reclassified under this section, it may revoke any special control or premarket approval requirement that was previously applied to the device. In addition, reclassification of specific device will result in reclassification of all devices within the same generic type.

2.16 Part 861: Performance Standards Development [23]

The FDA may determine performance standards of class II devices in accordance to special controls described in Section §860.7(b) to ensure safety and effectiveness of the device. This part implements Section 514 of the FDA Act for establishment, amendment, and revocation of performance standards applicable to medical devices.

Contents of Standards
Such performance standards established by FDA will address, but not be limited to:

(a) Device performance characteristics
(b) Design, components, and properties of device and its compatibility with other components
(c) Manufacturing and quality control procedures applicable to the device
(d) Testing all the devices by the manufacturer or testing by FDA or a third person to ensure conformity of the device to standard
(e) Publication of the results of test or tests of the device to show their conformity to standard
(f) Manufacturers' certification to purchasers or FDA for device conformity to standards
(g) Restrictions on the sale and distribution of the device, in accordance to Section 520(e) of the FDA Act
(h) Use of proper form and content of the label for installation, maintenance, operation, warnings, storage, transportation expiration dates, concerning statements for appropriate patient population, and for safe usage of devices

Performance Standards Development and Publication
The FDA will publish in the FEDERAL REGISTER a notice of a proposed rulemaking for the establishment, amendment, or revocation of any performance standards for a device. The FDA might either develop or may accept an existing or proposed standard to be published in their FEDERAL REGISTER. This notice will set forth the findings that the performance standards are appropriate and necessary for the safety and effectiveness of the device and/or for the reduced risk of illness or injury associated with the device. A notice under this section will be available for comments from interested persons not less than 60 days. If FDA receives a request for a change within 60 days of the publication of notice, upon consultation with the appropriate panel, it will either deny the request or give a notice for its intent to initiate a change in the classification.

Amendment or Revocation of a Standard
The FDA will provide for periodic evaluation of performance standards to determine their ability to reflect the recent advances in medical, scientific, or other technologies. FDA may amend or revoke by regulation the standard established, on its own or upon petition of an interested party. Any petition or proceedings to amend or revoke a performance standard shall be conducted in accordance with the rulemaking procedures of §10.30. This notice of proposed rulemaking to amend or revoke the standard, in addition, shall also set forth the proposed evidences for reduced risks or health benefits or illness to be eliminated from the proposed amendment or revocation.

Standards Advisory Committees
The FDA will establish advisory committees, to which proposed regulations may be referred for reports and recommendations. The members of the advisory committees established under this section shall include:

(a) Members selected in accordance with §14.82 and §14.84, except that no member may be a full-time FDA employee
(b) Nonvoting member representative of consumer interests
(c) Nonvoting member representative of interests of device manufacturing industry

The FDA will furnish the advisory committee with the data and information upon which the referred proposed regulation is based. After independently reviewing the materials provided, advisory committee shall submit a report and statement of reason/or basis for the recommendation on the proposed regulation, within 60 days of the referral. In the office of the Division of Docket Management, FDA, a copy of the report and recommendation will be publicly displayed.

2.17 Part 862-898: Medical Device Listing and Premarket Approval [7]

These parts of the Chapter I of Title 21 of FDA regulation sets forth the classification of medical devices that are in commercial distribution intended for human therapeutic or diagnostic use. A premarket notification is required to be submitted by a manufacturer for a device under Part 807, for establishment registration and device listing. This notification should identify the device for its description and section title in this part of the regulation. The classification of devices may not show precise description of every device that is or will be subjected to the regulation. In such instances, as required by §807.87, a manufacturer shall state why the device is substantially equivalent to other devices. To avoid duplicative listing, devices with more than one type of use (i.e., both as therapeutic and as diagnostic use) shall be listed only in one subpart. A device included in this part of regulation classified into class III (premarket approval) shall not be commercially distributed after the date mentioned in the regulation classifying the device, unless the device has been approved by FDA Act under Section 515.

Exemption from the Requirements of Premarket Approval
The requirement of premarket notification for a generic type of class I or II device as per Section 510(k) of the Act is exempted only if applicable to device with existing or reasonably foreseeable characteristics of commercial distribution within the generic type or, in the case of in vitro diagnostic devices, only if the misdiagnosis as a result of using the device would not be associated with morbidity or mortality. FDA has granted exemption for these class I and II devices from the requirement of premarket notification. However, the manufactures of these commercially distributed devices must still submit a premarket notification to FDA before introducing the device into interstate commerce.

Bibliography

1. U.S. Food and Drug Administration. 19 Sept. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPartFrom=800&CFRPartTo=1299. Accessed 22 Jun. 2020
2. FEDERAL REGISTER. The Daily Journal of the United States Government, www.federalregister.gov/agencies/food-and-drug-administration. Accessed 2 June 2020
3. Regulations. gov. www.regulations.gov. Accessed 13 Mar. 2020
4. Code of Federal Regulations. 18 Aug. 2016, www.archives.gov/federal-register/cfr. Accessed 24 Apr. 2020
5. Code of Federal Regulations list of Subjects. 1 Oct. 2019, www.archives.gov/federal-register/cfr/subjects.html. Accessed 18 May 2020
6. Electronic Code of Federal Regulations. 18 Jun. 2020, www.ecfr.gov/cgi-bin/ECFR?page=browse. Accessed 22 June 2020
7. CFR Title 21 – Food and Drugs: Parts 800 to 1299. 1 Apr. 2019, www.document-center.com/standards/show/21CFR(800-1299). Accessed 17 Jun. 2020

8. CFR Title 21 – Food and Drugs: Parts 800: General. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=800&showFR=1. Accessed 23 May 2020
9. CFR Title 21 – Food and Drugs: Parts 801: Labeling. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=801&showFR=1. Accessed 20 Jun. 2020
10. CFR Title 21 – Food and Drugs: Parts 803: Medical device reporting. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=803&showFR=1. Accessed 7 Apr. 2020
11. CFR Title 21 – Food and Drugs: Parts 806: Medical devices; reports of corrections and removals. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=806&showFR=1. Accessed 14 Mar. 2020
12. CFR Title 21 – Food and Drugs: Parts 807: Establishment registration and device listing for manufacturers and initial importers of devices. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=807&showFR=1. Accessed 18 Apr. 2020
13. CFR Title 21 – Food and Drugs: Parts 808: Exemptions from federal preemption of state and local medical device requirements. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=808&showFR=1. Accessed 20 Jun. 2020
14. CFR Title 21 – Food and Drugs: Parts 809: In vitro diagnostic products for Human use. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=809&showFR=1. Accessed 3 Jun. 2020
15. CFR Title 21 – Food and Drugs: Parts 810: Medical device recall authority. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=810&showFR=1. Accessed 9 May 2020
16. CFR Title 21 – Food and Drugs: Parts 812: Investigational device exemptions. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1. Accessed 26 May 2020
17. CFR Title 21 – Food and Drugs: Parts 814: Premarket approval of medical devices. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1. Accessed 19 Apr. 2020
18. CFR Title 21 – Food and Drugs: Parts 820: Quality system regulation. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=820&showFR=1. Accessed 23 May 2020
19. CFR Title 21 – Food and Drugs: Parts 821: Medical device tracking requirements. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=821&showFR=1. Accessed 9 Jun. 2020
20. CFR Title 21 – Food and Drugs: Parts 822: Postmarket surveillance. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=822&showFR=1. Accessed 17 May 2020
21. CFR Title 21 – Food and Drugs: Parts 830: Unique device identification. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=830&showFR=1. Accessed 11 May 2020
22. CFR Title 21 – Food and Drugs: Parts 860: Medical device classification procedures. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=860&showFR=1. Accessed 8 Jun. 2020
23. CFR Title 21 – Food and Drugs: Parts 861: Procedures for performance standards development. 1 Apr. 2019, www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=861&showFR=1. Accessed 11 Jun. 2020

EU 1907/2006 – Registration, Evaluation, Authorisation and Restriction of Chemicals

Indumathy Jagadeeswaran and Harini Sriram

1 Introduction

1.1 Regulation EC 1907/2006

Regulation (EC) no 1907/2006 of the European Parliament and the Council of the European Union, concerning the registration, evaluation, authorization, and restriction of chemicals (REACH), in regard to the treaty establishing the European Community, particularly Article 95, in regard to the Commission's proposal, in regard to the European Economic and Social Committee's opinion, execution in accordance with the procedure laid down in Article 251 of the Treaty, European Commission (EC), comprises of regulations which work to ensure the safety of the patient and efficacy of the device [1]. This regulation ensures a high level of protection of human health and environment as well as the free movement of substances, with the goal of achieving sustainable development. The European Union, in pursuant to the implantation plan adopted on 4 September 2002 at Johannesburg World Summit, is aiming to achieve sustainable development where chemicals are produced and used with minimal adverse effects on human health and the environment [1].

I. Jagadeeswaran (✉)
Department of Biological Sciences, Southern Methodist University, Dallas, TX, USA

H. Sriram
National Dental Centre Singapore, Singapore, Singapore

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_13

1.2 Establishment of Compliance with REACH Regulation

An important objective for establishing REACH is to encourage and ensure that substances of high concern are eventually replaced by less dangerous substances or economical technologies where viable alternatives are available. This regulation does not affect the application of directives on worker protection and the environment, and employers are required to eliminate or substitute the dangerous substances, wherever possible to protect the health and safety of their workers. The key components of REACH are [1, 2]:

- Registration.
- Evaluation.
- Authorization.
- Restriction.
- REACH safety datasheet.

This regulation requires manufacturers and importers to generate information on substances, to assess their risks, and to develop and recommend appropriate risk management measures. The European Chemical Agency (Agency) requires manufactures and importers to submit this information for registration, and only registered substance is allowed to circulate on internal market. The Agency and member states shall evaluate whether the registration is in compliance with the requirements of this regulation. Such information submitted for registration can also be used by the Agency to initiate authorization or restriction procedures under this regulation. Authorization provisions ensure good functioning of internal market and assure that the very high-risk substances are properly controlled. The EC will provide authorization for a substance to be placed in market and usage. Restriction provisions allow manufacturing, placing on market, and use of substance with subject to total or partial ban or other restrictions [1, 2].

1.3 Purpose and Scope [1]

The primary strategy of the regulation is to ensure safety of human health and environment, including promotion of alternative methods for hazard assessment and free circulation of substances, as specified in Article 3. This regulation is based on principle that it is for manufacturers, importers, and downstream users to ensure that they manufacture, place on market, or use such substances that do not adversely affect human health or environment.

1. This regulation does not apply to the following:

   (a) Radioactive substances and mixtures that are in the scope of Council Directive 96/29/Euratom of 13 May 1996 which has laid down the primary safety standards for the protection of workers' health. It also takes public

health into account ensuring against the danger arising from ionizing radiation.

(b) Substances, on their own, in a preparation or in an article, which are in subject to customs supervision which do not undergo any treatment or processing, which are in temporary storage or in a free zone or free warehouse with a re-exportation or in transit view.
(c) Non-isolated intermediates.
(d) Dangerous substances and dangerous substance in preparations by air, road, sea, rail, or inland waterways transportation.
(e) Waste as defined in Directive 2006/12/EC of the European Parliament and Council of 5 April 2006, which is not a substance, mixture or article within the meaning of Article 3 of this Regulation.
(f) In specific cases where, the substances on their own or in a preparation or in an article are interest of to defense, the member states may allow for exemptions from this regulation.

2. This regulation shall apply without prejudice to:

(a) Community workplace and environmental legislation, including Council Directive 89/391/EEC of 12 June 1989 on the introduction of measures to encourage improvements in the safety and health of workers at work [3]; Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control [4]; Directive 98/24/EC and Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy [5]; and Directive 2004/37/EC.
(b) Directive 76/768/EEC testing involving vertebrate animals.

3. The provisions of Title II, V, VI, and VII of this regulation shall not apply to the extent that a substance is used:

(a) In medicinal products for human or veterinary use within the scope of Regulation (EC) No 726/2004, Directive 2001/82/EC on the Community code relating to veterinary medicinal products [6] and Directive 2001/83/EC on the Community code relating to medicinal products for human use [7].
(b) Food or feeding stuffs as defined in Regulation (EC) No 178/2002 including when they are used as a food additive (89/107/EEC), flavoring (Directive 88/388/EEC and Decision 1999/217/EC), additive (Regulation (EC) No 1831/2003), or animal nutrition (Directive 82/471/EEC) in foodstuffs or feeding stuffs within the scope of these Directives.

4. The provisions of VI of this regulation shall not apply to the following preparations in the finished state intended for final user:

(a) Medicinal products for human or veterinary use, within the scope of Regulation (EC) No 726/2004 and Directive 2001/82/EC and as defined in Directive 2001/83/EC.
(b) Cosmetic products as defined in Directive 76/768/EEC.

(c) Medical devices which are invasive or used in direct physical contact with the human body in so far as Community measures lay down provisions for the classification and labelling of dangerous substances and preparations which ensure the same level of information provision and protection as Directive 1999/45/EC.
(d) Food or feeding stuffs as defined in Regulation (EC) No 178/2002 including when they are used as a food additive (89/107/EEC) [8], flavoring (Directive 88/388/EEC [9] and Decision 1999/217/EC [10]), additive (Regulation (EC) No 1831/2003 [11], or animal nutrition (Directive 82/471/EEC) [12] in foodstuffs or feeding stuffs within the scope of these Directives.

2 Registration of Substances [1]

2.1 General Obligation to Register and Information Requirements

The stakeholders (manufacturers or importers) of a substance on its own, in articles or in preparations, shall submit a registration to the Agency, if they meet any of the following conditions:

(a) In quantities of 1 ton or more per year.
(b) If the polymer consists of 2% weight by weight (w/w) or 0.1% weight by weight (w/w) for the substance present in articles.

These substances shall not be manufactured or placed on market unless they have been registered subject to articles 6, 7, 21, and 23 of this regulation. Registration of article is exempted if the substance in the article has already been registered for that use. Submission for registration shall be accompanied by the fee required by Title IX of this regulation.

2.2 Exemption to Register for Product and Process-Oriented Research or Development (PPORD)

This general obligation to register is exempted for a period of 5 years for the substances manufactured or imported for the purpose of product and process-oriented research or development (PPORD). However, the manufacturer or importer or producer of articles shall notify the agency regarding their identity, identity of substance, its classification and labelling, estimated quantity, and list of customers. This notification shall be accompanied by the fee required in accordance with Title IX. The agency will check the completeness of the information submitted and shall assign a notification number and date, which shall be the receipt of notification.

They agency might ask for additional information from the notifier or shall impose some conditions to ensure safe handling of the substance or the preparation or article. The agency shall also communicate this information to the concerned member state(s) authority. The 5-year period shall begin at receipt of notification at the Agency. The manufacturer or importer or producer of articles shall request for extension for the substance justifying their exclusive use in research and development of medicinal products for human and veterinary programmed. The Agency shall make decision on extending the exemption period considering the comments from Member state(s) authorities, for any 5 years or further up to 10 years for the substance that are not placed on the market.

2.3 Information to Be Submitted for General Registration Purposes (Article 10)

For the purpose of registration required by article 6 or 7(1) or 5, the manufacturer or importer or producer of articles shall notify the following information to the Agency:

A. **A technical dossier including:**

(i) The identity and contact details of the manufacturer or importer or producer of articles as specified in section 1 of Annex VI.
(ii) Registration number in article 20(1).
(iii) Identity of the substance (section 2 Annex VI) and classification of substance (section 4 Annex VI).
(iv) Estimated quantity as specified in section 3.1 of Annex VI.
(v) Brief description on the safe use of the substance or substance in the article specified in section 5 of Annex VI and use(s) of the article(s).
(vi) Study summaries of the information derived from the application of Annexes VII and XI.
(vii) Robust study summaries of the information derived from the application of Annexes VII to XI, if required under Annex I.
(viii) An indication of information which has been reviewed by an assessor with appropriate experience.
(ix) Proposals for testing where listed in Annexes IX and X.
(x) For substances in quantities of 1 to 10 tons, exposure information as specified in section 6 of Annex VI.
(xi) A request by the manufacturer or importer with justification, if any information shall not be made available on the Internet in accordance with article 77(2)(e), given his or other party's commercial interest.

B. **A chemical safety report required under Article 14, with relevant use and exposure categories**

When a substance is intended to be manufactured by one or more manufacturers and/or imported by one or more importers and/or is subject to registration under Article 7 of this regulation, the following shall apply:

(i) One registrant shall submit the information in Article 10(a)(iv), (vi), (vii), and (ix) and any relevant indication under Article 10(a)(viii) to the Agency (hereinafter referred to as "the lead registrant") acting with the agreement of the other assenting registrant(s).
(ii) Each registrant shall subsequently submit separately the information specified in Article 10(a)(i), (ii), (iii), and (x) and any relevant indication under Article 10(a)(viii).
(iii) The registrants may decide themselves whether to submit the information specified in Article 10(a)(v) and (b) and any relevant indication under Article 10(a)(viii) separately or whether one registrant is to submit this information on behalf of the others.

But the information specified in Article 10(a)(iv), (vi), (vii), and (ix) for the purposes of registration shall be submitted by each registrant within his tonnage band. The physicochemical, toxicological, and ecotoxicological information that is relevant and available to the registrant shall be specified in Article 10 under points (vi) and (vii). As soon as the quantity of a substance per manufacturer or importer reaches the next tonnage threshold, the Agency must immediately be informed with necessary information as required by this regulation.

A registrant may also submit the information specified in Article 10(a)(iv), (vi), (vii), and (ix) separately, along with dossier if:

(i) He disagrees with the selection of this information with the lead registrant.
(ii) Filling jointly would be disproportionately costly for him.
(iii) Joint filling would lead to disclosure of commercially sensitive information.

2.4 General Requirements for Generating Information on Intrinsic Property of Substances

The intrinsic properties of substances can be produced with other test methods as per the conditions set out in Annex XI. The information on human toxicity should be generated through the alternative methods such as in vitro methods or qualitative or quantitative structure-activity relationship models, whenever possible to avoid the use of vertebrate animals for testing. The test methods in vertebrate animals shall be regularly reviewed and improved to reduce the testing and the number of animals involved. Commission Regulation shall be adopted in accordance with the procedure referred to in Article 133(4), and the Annexes of this Regulation, so as to

replace, reduce, or refine animal testing. Ecotoxicological and toxicological tests and analyses shall comply with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognized as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable.

2.5 Chemical Safety Report and Recommended Risk Reduction Measures

A chemical safety assessment shall be performed, and a chemical safety report shall be completed for all substance (in quantities of 10 tons or more per year per registrant) subject to registration, without prejudice to Article 4 of Directive 98/24/EC. A chemical safety assessment shall be conducted for either each substance on its own or in a preparation or in an article in accordance with Annex I of this regulation.

A chemical safety assessment shall be exempted if the concentration of substance is less than the lowest of any of the following:

(i) Concentration defined in Article 3(3) of Directive 1999/45/EC.
(ii) Concentration limits in Annex I to Directive 67/548/EEC.
(iii) Concentration limits in Part B of Annex II and Annex III to Directive 1999/45/EC.
(iv) Concentration limits in the classification and labelling inventory established under Title XI of this Regulation.
(v) 0,1% weight by weight (w/w), if the criteria in Annex XIII of this Regulation is met.

A chemical safety assessment of a substance shall include the following steps:

(i) Human health hazard assessment.
(ii) Physicochemical hazard assessment.
(iii) Environmental hazard assessment.
(iv) Persistent, bioaccumulative, and toxic (PBT) and very persistent and very bioaccumulative (vPvB) assessment.

Based on the results from the chemical assessment steps, the registrant concludes that the substance meets the criteria for classification as dangerous in accordance with Directive 67/548/EEC or is assessed to be as a PBT or vPvB. The exposure scenarios (where appropriate the use and exposure categories), exposure assessment, and risk characterization for all identified uses of the registrant shall also be addressed and included in the chemical safety assessment. Any registrant shall identify and apply the appropriate measures to adequately control the risks identified in the chemical safety assessment and, where suitable, recommend them in the safety data sheets which he supplies in accordance with Article 31. Any registrant required to conduct a chemical safety assessment shall keep his chemical safety report

available and up to date. The chemical safety report need not include consideration of the risks to human health from the end uses (a) in food contact materials within the scope of Regulation (EC) No 1935/2004**1** and (b) in cosmetic products within the scope of Directive 76/768/EEC.

2.6 Data Sharing and Avoidance of Unnecessary Testing

This regulation tries to avoid animal testing and limits the duplication of other tests. The sharing and joint submission for the purposes of this regulation enables the registrants to refrain from exchanging concern technical data and their market behaviors (such as production or sales volume, production capacity, import volume, or market shares). If a substance has already been registered at least 12 years (in accordance to Article 26(3)) previously, a new registrant shall be entitled to refer to the study summaries or robust study summaries under this regulation, provided that he can show that the substance that he is now registering is the same as the one previously registered, including the degree of purity and the nature of impurities. In this case, if the substance has previously been registered for less than 12 years, the new registrant might request the previous registrant for information specified in Article 10 under points (vi) and (vii) in order to register. In such situations, the previous registrant and the potential registrant shall share the costs of data generation in accordance with Article 77(2)(g) of this regulation. The new registrant shall access the full study reports, given that the previous registrant(s) have given permission to refer for the purpose of registration. However, a new registrant shall not refer to such studies to provide the required information on substance identity (section 2 of Annex VI).

2.7 Registration Process

- On submission of notification for registration of a substance on its own or in a preparation or in an article to the Agency, the Agency shall assign a submission number and submission date (date of receipt) to each registration.
- The Agency shall check the completeness of each registration in order to ascertain that all elements required under this regulation and the appropriate registration fee referred in this regulation have been provided. But this completeness check does not include assessment of quality or adequacy of any data or justifications submitted.
- The Agency shall undertake the completeness check within 3 weeks or within 3 months (for in-phase substances in accordance with Article 23).
- If the registration is incomplete, the Agency shall inform the registrant, regarding further information required to be submitted for the registration to be complete within the stipulated time window.

- The registrant shall complete his registration and submit it to the Agency within the deadline. Failure to complete the registration within the deadline set shall pose rejection of the registration. The registration fee shall not be reimbursed in such instances.
- On the registrant completing his registration, the Agency shall perform further completeness check along the information provided. On completion of registration, the Agency without delay shall communicate the registration number and date to the registrant, which shall be used for all subsequent correspondence.
- The registrant may start the manufacture or import of a substance or production or import of an article if there is no indication to the contrary from the Agency within 3 weeks after receipt by the Agency, without prejudice to Article 27(8).
- The Agency shall also notify the competent authority of relevant Member State(s) within 30 days of the submission date, regarding the registration relevant information available in the Agency database.
- Following registration, it is the responsibility of the registrant to update his registration without undue delay with the relevant new information regarding the substance along the relevant part fee in accordance with this regulation. The Agency shall intimate relevant competent Member state authority regarding the update available in the database.

3 Evaluation [1]

3.1 Dossier Evaluation

The agency shall examine testing proposal submitted in a registration or a downstream user report for substance-relevant information specified in Annexes IX and X. Substances which have or may have PBT, vPvB, sensitizing and/or carcinogenic, mutagenic, or toxic for reproduction (CMR) properties or substances classified as dangerous according to Directive 67/548/EEC above 100 tons per year with uses resulting in widespread and diffuse exposure shall be given priority for evaluation.

The name of the substance, hazard end-point of the proposed vertebrate testing (testing proposal), and the set deadline (usually 45 days) for third party to submit scientifically valid information shall be published by the Agency on its website. Such scientifically valid information and studies that address relevant substance and hazard end-point, submitted by the third party, shall be considered by the Agency in preparing its decision in accordance to this regulation. In accordance to the procedures laid down in Articles 50 and 51, the Agency shall draft one of the following decisions:

(a) A decision requiring the concerned registrant(s) or downstream user(s) to perform the proposed test and submit the study summary (or the robust study summary if required by Annex I) within a set deadline.

(b) A decision in accordance with point (a), but modifying the conditions under which the test is to be carried out.
(c) A decision in accordance with points (a), (b), or (d) but requiring registrant(s) or downstream user(s) to carry out one or more additional tests in cases of non-compliance of the testing proposal with Annexes IX, X, and XI.
(d) A decision rejecting the testing proposal.
(e) A decision in accordance with points (a), (b), or (c), if several registrants or downstream users of the same substance have submitted proposals for the same test, giving them the opportunity to reach an agreement on who will perform the test on behalf of all of them and to inform the Agency accordingly within 90 days. If the Agency is not informed of such agreement within such 90 days, it shall designate one of the registrants or downstream users, as appropriate, to perform the test on behalf of all of them.

Compliance Check of Registrations

To verify its compliance with the regulation, the Agency may examine any registration for:

(a) That the requirements of Articles 10, 12, and 13 and with Annexes III and VI to X are submitted in the technical dossier (in pursuant to Article 10).
(b) That the adaptations of the standard information requirements and the related justifications submitted in the technical dossier(s) are in compliance with the rules governing such adaptations set out in Annexes VII to X and with the general rules set out in Annex XI.
(c) That any required chemical safety assessment and chemical safety report comply with the requirements of Annex I and that the proposed risk management measures are adequate.
(d) That any explanation(s) submitted in accordance with Article 11(3) or Article 19(2) have an objective basis.

In accordance to Article 50 and 51 of this regulation, within 12 months of the start of compliance check, the Agency may prepare a draft decision requiring the registrants to submit any further information within a stipulated deadline, required to bring the registration into compliance. To ensure the dossier compliance with this regulation, the Agency will select no lower than 5% of the total dossier received for each tonnage band. The list of dossiers checked by the Agency for compliance with this regulation shall be made available to the Member States competent authorities. The Agency shall examine any information submitted in consequence of decision taken under Article 40 or 41. On completion of dossier information, the agency shall notify the Commission and the competent authorities of the Member States of the information obtained and any conclusions made.

3.2 Substance Evaluation

To ensure harmonized approach, the Agency in cooperation with the Member states develops criteria for prioritizing substances grounded on risk-based approach. The criteria shall consider:

(a) Hazard information, for instance, structural similarity of the substance with known substances of concern or with substances which are persistent and liable to bio-accumulate, suggesting that the substance or one or more of its transformation products has properties of concern or is persistent and liable to bio-accumulate.
(b) Exposure information.
(c) Tonnage, including aggregated tonnage from the registrations submitted by several registrants.

Based on these criteria, the Agency shall compile a draft community rolling plan which shall cover a period of 3 years and shall specify the substances (based on their risks to human health or environment) to be evaluated each year. A draft annual update to the rolling plan will be submitted by the Agency to the Member States by 28 February each year. Based on the opinion from the Member State Committee (set up under Article 76(1)(e)), the Agency shall adopt the final Community rolling action plan and publish the plan on its website, identifying the Member State who will carry out the evaluation of the substances listed therein as determined according to Article 45.

Competent Authority

The Agency shall be responsible for coordinating the substance evaluation process and ensuring that substances on the Community rolling action plan are evaluated. In doing so, the Agency shall rely on the competent authorities of Member States. The competent authorities may appoint another body to act on their behalf to carry out an evaluation of a substance. A Member State may notify the Agency at any time, if a substance has priority for evaluation, not on the Community rolling action plan. The Agency shall decide whether to add this substance to the Community rolling action plan on the basis of an opinion from the Member State Committee. If the substance is added to the Community rolling action plan, the proposing Member State, or another Member State who agrees, shall evaluate that substance.

If the competent authority considers that further information is required, it shall prepare a draft decision, stating reasons, requiring the registrant(s) to submit the further information within a set deadline for its submission. A draft decision shall be prepared within 12 months of the publication of the Community rolling action plan on the Agency's website for substances to be evaluated that year. The decision shall be taken in accordance with the procedure laid down in Articles 50 and 52. The competent authority shall finish its evaluation activities within 12 months of the

start of the evaluation of the substance or within 12 months of the information being submitted under paragraph 2 and notify the Agency accordingly. If this deadline is exceeded, the evaluation shall be deemed finished.

Follow-up to Substance Evaluation

Once the substance evaluation has been completed, the competent authority shall consider how to use the information obtained from this evaluation for the purposes of Article 59(3), Article 69(4), and Article 115(1). The competent authority shall inform the Agency of its conclusions as to whether or how to use the information obtained. The Agency shall in turn inform the Commission, the registrant, and the competent authorities of the other Member States.

Adoption of Decisions

- The Agency shall notify its draft decision in accordance with Article 40 or 41, together with the comments of the registrant, to the competent authorities of the Member States.
- Within 30 days of circulation, the Member States may propose amendments to the draft decision to the Agency.
- If the Agency does not receive any proposals, it shall take the decision in the version notified under paragraph 1.
- If the Agency receives a proposal for amendment, it may modify the draft decision.
- The Agency shall refer a draft decision, together with any amendments proposed, to the Member State Committee within 15 days of the end of the 30-day period referred to in paragraph 2.
- The Agency shall forthwith communicate any proposal for amendment to any registrants or downstream users concerned and allow them to comment within 30 days.
- The Member State Committee shall take any comments received into account.
- If within 60 days of the referral, the Member State Committee reaches a unanimous agreement on the draft decision, the Agency shall take the decision accordingly.
- If the Member State Committee fails to reach unanimous agreement, the Commission shall prepare a draft decision to be taken in accordance with the procedure referred to in Article 133(3).
- In accordance with Articles 91, 92, and 93, an appeal may be brought against Agency decisions.

Publication of Information on Evaluation

The Agency by 28 February of each year shall publish on its website a report on the progress made over the previous calendar year toward discharging the obligations incumbent upon it in relation to evaluation. This report shall include, in particular, recommendations to potential registrants in order to improve the quality of future registrations.

4 Authorization [1]

4.1 Requirement and Considerations for Substitution

The purpose of authorization is to properly maintain dangerous substances in the market with risk controls and finding lesser dangerous substances/technologies to replace them while considering the economic and technical feasibility and viability. This responsibility lies for the manufacturers, importers, and downstream users that apply for and claim authorization.

Article 56 talks about the general provisions for the requirement of authorization procedure. A substance included under Annex XIV of this regulation is not to be placed on the market or used by the manufactures, importer, or downstream user without authorization. The exemptions are made when the substance/mixture's use has been authorized, or it has been exempted from authorization considering the community legislation governs the use of the substance and the risk control measures. The exemption also holds if the date until which the substance can be placed and used in the market has not been reached and 18 months from this date once the extension for the authorization has been submitted. The immediate downstream user can be authorized to use the regulated substance. This use has to be the same as given in the authorization application submitted. These exemptions do not apply for the use of the substance in scientific research and development, and for the product and process-oriented research, the maximum quantity exempted has to be provided by Annex XIV. Substances used as plant protection products [13], biocidal products [14], motor fuels [15], and fuel in mobile or fixed combustion plants of mineral oil products and use as fuels in closed systems do not follow the exemptions mentioned above. The substances are to be authorized when classified under Article 57 as hazardous to human health, and the exemptions provided do not apply for their use in cosmetic products [16] and food contact materials [17]. Persistent, bio-accumulative, and toxic substances used in preparations containing concentration below 0.1% weight/weight and along with substances with lowest concentration limits [18, 19] classified as dangerous are subject to authorization without exemptions.

Article 57 specifies the substances to be included in Annex XIV following the procedures in Article 58. The substances included are carcinogenic category 1 or 2 [20], mutagenic category 1 or 2 [20], and toxic for reproduction category 1 or 2 [20].

The substances classified under Annex XIII of this regulation as persistent based on the half-life in marine water (higher than 60 days), fresh- or estuarine water (higher than 40 days), marine sediment (higher than 180 days), fresh- or estuarine water sediment (higher than 120 days), or in soil (higher than 120 days) are to be included in this Annex. The substances bioaccumulating with bioaccumulation factor greater than 2000 and toxic substances are included as well. A substance with observed toxicity of long term no-observed effect concentration (Noec) for marine and freshwater organisms is less than 0.01 mg/ml and showing chronic toxicity is identified as T, R48, or Xn and R48 [20]. A substance classified as very persistent when the half-life of the substance in marine/fresh/estuarine water or in marine/fresh/estuarine water sediment or in soil is higher than 60 days, 180 days and 180 days respectively. The very bioaccumulative substances with bioaccumulation factor more than 5000 are included in Annex XIV. Annex XIV also includes substances that have endocrine-disrupting properties and are persistent, bioaccumulative, and toxic in nature and do not follow the criteria laid out above but are scientifically proven to have adverse effects on human health and environment.

The inclusion of a substance in Annex XIV (Article 58) shall follow the regulatory procedure laid out by the Commission along with the Scrutiny Committee formed by the representatives of the Member States chaired by representative of the Commission [21]. Annex XIV must contain the identity of the substance such as name or other identifier, molecular and structural information, composition, degree of purity, impurities, additives, etc. [22]. The intrinsic property of the substance given by Article 57 has to be included in the Annex. The date (sunset date) from which the substance is placed on the market and its use is authorized. The date or dates before the sunset date by which the authorization application must be received for the continued use of the substance in the market after the sunset date is reached. The review period for the use of the substance wherever appropriate also has to be included. The exemptions from authorization for use/category of use for the substance also have to be mentioned with the basis of these exemptions. The substances to be included are prioritized by the Agency along with the Member State Committee based on their persistent, bioaccumulative, and toxic properties, wide dispersive use, or high volume. The number of substances and the dates mentioned above have to account for the Agency's ability to handle the applications. The first set of priority substances to be included in the Annex recommended by the Agency was included by 1 June 2009, and further inclusions are done every second year. The Agency has to publish the substances to be included in the Annex with public access at free of cost over the Internet with comments enabled before recommending to the Committee. With the comments received from interested parties within 3 months of the publication, the Agency can update its recommendation. The substances included in the Annex shall not be subjected to new restrictions under Title VIII when used on its own or in a preparation can possess risk to human health and environment. The substances can be subjected to new restrictions when its presence in an article proves as risk. The substances prohibited from all uses as per Title VII or by Community legislation shall not be included in the Annex or shall be removed.

The substances which do not fulfill the criteria mentioned in Article 57 resulting from a new information are to be removed.

The procedure for identification of substances referred to in Article 57 is laid out under Article 59 together with the candidate list for inclusion in Annex XIV. The Committee can ask the Agency to prepare dossier with the information on harmonized classification, identification, and restrictions (Annex XV) and make it available to the Member States. Any Member State can prepare and forward the dossier to the Agency, and the Agency has to make it available within 30 days of receipt. The Agency has to communicate the preparation of the dossier and invite other Member States and all other interested parties to comment within a deadline which is ideally within 60 days. If no comment is received, the Agency can recommend the inclusion of the substance in the list. When comments are received, the Agency has to refer the dossier to the Member State Committee within 15 days before the 60-day deadline. The Member State Committee reaches a unanimous agreement within 30 days, and the Agency shall include the substance in its recommendation list. When a unanimous agreement is not arrived, the Commission shall prepare a draft proposal on identification of substance to be submitted to the European Parliament and the Council for review. If no opposition is offered within 3 months of the draft submission, then the draft shall be adopted by the Commission and published on its website without delay.

4.2 Granting of Authorizations

Article 60 advices on granting of authorizations. The Commission is held responsible for taking decisions on applications and authorizations. The authorization is granted to the use of substance possessing risk to human health or environment in Annex XIV provided these risks are controlled and documented in chemical safety report with the opinion of the Committee of Risk Assessment [23]. It shall note the discharges, emissions, and losses, including risks arising from diffusion and dispersive uses while granting authorization. The risks to human health from use of a substance in medical device, active implantable medical devices, or in vitro diagnostic medical devices shall not be considered by the Commission [24–26]. This lenience is not given for substances listed in Article 57 for which the threshold exposure levels and likelihood and severity of the event occurring due to the physicochemical properties of the substance cannot be determined. The persistent, very persistent, bioaccumulative, very bioaccumulative, endocrine disrupting, and toxic substances cannot be given any exceptions with respect to controlled risk measures stated above. In this case, an authorization can only be granted if the socioeconomic benefits of the use of the substance are greater than the risk to human health or environment and no alternative substance or technologies are available. The decision is made considering the opinions of the Committee for Risk Assessment and Socioeconomic Analysis along with the appropriateness and effectiveness of the risk management measures proposed, socioeconomic benefits, socioeconomic

implications arising from refusal of authorization, analysis of alternatives or substitution plans submitted, and information on the risks to human health or environment from alternative substances or technologies. The Commission shall look into all relevant aspects of the suitable alternative substances or technologies including whether this transfer could reduce overall risks given the appropriateness and effectiveness of risk management measures and technical and economic feasibility of these alternatives. The use of the substance shall not be authorized if it involves relaxation of restriction set in Annex XVII. The grant of authorization is only possible when the application is confirming with the application requirement set in Article 62 of this regulation. The authorizations can be dependent on time-limited review with monitoring with the duration determined on a case-by-case basis. The authorization shall include the person to whom the authorization is granted, identity of the substance, the use for which the authorization is granted, any conditions under which authorization is granted, time-limited review period, and monitoring arrangement. The holder of authorization shall always ensure the exposure is reduced to as low technically and practically as possible.

Review of Authorizations

The review process for these authorizations is done according to Article 61 of this regulation.

- The validity of the authorization is granted until the Commission decides to amend or withdraw it for review unless the holder of authorization submits a review report 18 months before the expiry of time-limited review period.
- The holder shall submit an update of alternatives analysis, relevant research, and development activities done by the applicant and substitution plan.
- A substitution plan shall be submitted when a suitable alternative is available with timetable for proposed actions.
- When the holder can control the risk, then a chemical safety report is needed, and when risks cannot be controlled, an update to the socioeconomic analysis in the original application shall be given.
- Any updates to the elements of the original application have to be communicated in this review. The authorizations can be reviewed whenever the circumstances of the original authorization have changed affecting the risk to human health or environment or socioeconomic impact and suitable substitutes are available.
- The Commission sets a deadline by which the holder can submit further information required for review. The Commission can amend or withdraw the authorization under the changed circumstances with all the necessary information about these changes submitted by the holder of authorization.
- The Commission can decide to suspend the authorization pending review when there is serious and immediate risk for human health or environment.
- When the environmental quality standards and environmental objectives [27, 28] are not met, the authorization for the use of the substance can be reviewed, and

also if use of a substance is subsequently restricted/prohibited as persistent organic pollutant, then the authorization can be withdrawn by the committee [29].

Applications for Authorizations

The information regarding the application of authorization is given under Article 62 of this regulation. The application shall be submitted to the Agency. The application can be submitted by the manufacturer(s), importer(s), and/or downstream user(s) of the substance. An application can be submitted by more than one person. The application can include one or a group of substance with similar physicochemical, toxicological, and ecotoxicological properties for one or more uses. The applicant can submit application for own use and for uses for which the substance is placed on the market. The application shall include the identity of the substance(s), the name and contact detail of the person(s) submitting the application, a request for authorization for the specific use of the substance and use of preparation in which the substance is incorporated, a chemical safety report (unless submitted before as part of registration) mentioning the risks to human health or environment arising due to the intrinsic properties of the substance, analysis for the alternative substance or technology with information on research and development activities by the applicant, and a substitution plan with timetable when suitable alternatives are available for the substance in question. Additionally, the substance can include socioeconomic analysis and a justification for not considering risks to human health and environment through emissions of substance from a permitted installation [15] and discharges of the substance from point source [30]. The application shall not include risks to human health arising from use of the substance in medical device [24–26]. The application shall include the appropriate fee required as given under Title IX of this regulation. The subsequent applications are submitted as per Article 63. A subsequent application is filed for parts of the existing application such as chemical safety report, analysis of alternative to the applied substance, and substitution plan for the suitable alternatives proposed and socioeconomic analysis. This subsequent applications provision applies for already granted authorization. The subsequent application shall also update the information in the original application.

Procedure for Authorization Decisions

The procedure for decisions on authorization is listed in Article 64. Firstly, the Agency shall acknowledge the receipt of application with date. The Agency's Committees for Risk Assessment and Socioeconomic analysis shall give their opinions on the draft within 10 months of receipt of application. The Agency shall make information on use of the substance publicly accessible at free of cost as soon as the application is received with the deadline for alternative substances or technologies submissions. The Committees shall check that the application shall include all

information asked for as per Article 62. The Committees shall consult with each other and request for additional information from the applicant and consider all information submitted by third parties. The Socioeconomic Analysis Committee requires for the applicant or third parties to submit additional information on possible alternative substance or technologies within a specified time period. The draft opinions shall contain Committee for Risk Assessment and Committer for Socioeconomic Analysis. The Agency shall communicate the draft opinions to the applicant by end of deadline and considered to be received by the applicant within 7 days of sending. The applicant shall give in writing if he/she wishes to comment within 1 month of receipt of draft opinion. When no comment is made, the Agency shall send the opinions to the Commission, the Member States, and the applicant within 15 days of end of period for applicant's comment or within 15 days of receipt of notice of "no comment" from applicant. The applicant shall send his written arguments/comments to the Agency within 2 months of receipt of draft opinion, and the Committee shall consider the comments and make their final opinions within 2 months of receipt of applicant's arguments. The Agency shall send the opinions with written argumentations to the Commission, the Member States, and applicant in further 15 days. The Agency decides which part of opinions and attachments to be published for public access on its website. When subsequent applications are submitted to the original application, the Agency can consider the application together within the deadlines for the original application. The Commission shall decide on the draft authorization within 3 months after receiving the Agency's opinion. The final decision on granting or refusal of the authorization is within a time limit determined by urgency by the advice of the Commission or sometimes by voting. The Commission decisions with the authorization number and reason for the decision shall be published in the Official Journal of the European Union and made available publicly database which is kept up to date by the Agency. For subsequent application, the deadline is shortened by 5 months.

4.3 Obligation of Holders of Authorizations

The obligations of holders of authorization are described in Article 65. The holders of authorization and the downstream users shall include the authorization number of the substance on the label before placing the substance or preparation including the substance on the market for its authorized use as soon as the authorization number is published. The downstream users shall notify the Agency within 3 months of start of the supply of the substance. The Agency shall document the downstream users through a register and maintain it up to date. This register has to be accessible for competent authorities of the Member States.

5 Restrictions on the Manufacturing, Placing on the Market, and Use of Certain Dangerous Substances, Preparations, and Articles [1]

5.1 General Provisions for Introducing New and Amending Current Restrictions

The provisions for the restrictions for the substances to be placed on the market and be used are given under Article 67 of this regulation. Annex XVII specifies the restrictions and conditions under which the restrictions can be relaxed for product and process-related research and development along with the maximum exemption quantity. The substance or the preparation of the substance included in the Annex XVII with a restriction shall not be placed on the market or used beyond the conditions mentioned in the Annex. For example, chloroform shall not be used in concentrations equal to 0.1% or more by weight for public sale and/or in diffusive purposes such as surface cleaners or fabric cleaners. This restriction does not be considered for use of the substance in scientific research and development. The restrictions do not cover the use of the substances in cosmetic products as it is already defined by a different directive [16]. The Commission is responsible for compiling and publishing the inventory of the restrictions by 1 June 2009. A Member State shall maintain record of existing and stringent restrictions in Annex XVII after having notified till 1 June 2013.

The restriction process is detailed under Article 68. An unacceptable risk to human health or environment occurs from manufacture, placing on the market, or use of a substance. Annex XVII has to be amended with new restrictions altering the current restrictions [21]. These restrictions shall be made considering socioeconomic impact and availability of alternatives. The use of substance as onsite isolated intermediate can be exempted from the amendment. For substances or preparations classified as carcinogenic, mutagenic, or toxic to reproduction category 1 or 2 and used by consumers, the Commission proposes the restrictions and amended by the regulatory procedure laid out by Commission along with the Scrutiny Committee formed by the representatives of the Member States chaired by representative of the Commission [21], and the following Article does not apply.

5.2 Restriction Process

Preparation of Restriction Proposal

- When the manufacture, placing on the market, or use of a substance or its preparation proves as risk to human health or environment and these risks are not adequately controlled, then the Commission and the Member States can request the Agency to prepare Dossier with restriction proposal, information on

alternatives, justification for the restriction, and socioeconomic assessment following Annex XV of this regulation.
- The Agency can also prepare the dossier after the sunset date when it considers the use of substance or its preparation generates risk which is not adequately controlled. The Agency has to suggest restrictions to initiate the restriction process if the dossier proves more actions are needed within 12 months of the Commission's request.
- The Member State is responsible for preparing and submitting the dossier for restrictions when the substance is not included in the list maintained by the Agency within 12 months after notifying the Agency to initiate the restrictions. The Agency or Member States can refer to any dossiers, chemical safety reports, and risk assessments submitted for other purposes and also can request other agencies under the Community law for this information.

Agency Opinion: Committee for Risk Assessment and Socioeconomic Analysis

- The Committee for Risk Assessment and Socioeconomic Analysis shall oversee if the dossiers submitted by the Agency or the Member State conform with the requirements within 30 days of submission. Any conform problems shall be communicated to the Agency or the Member States within 45 days of receipt of the dossier with reasons and corrected within 60 days of receiving the reasons from the Committee.
- The Agency shall publish the opinion of the Commission of Member State to initiate the restriction procedure and inform the registrant of the same. The Agency is responsible for maintaining the list of substances for which dossiers are planned or underway. A substance included in this list shall not have any other dossier.
- If an existing restriction has to be re-examined, it has to be decided by the Commission assisted by an advisory committee composed of the representatives of the Member States and chaired by the representative of the Commission. This representative has to submit a draft of measures to be taken to the Committee, and the decision has to be taken within a time limit based on the urgency based on the evidence presented and may be through a voting system [21].
- The Agency shall make the dossiers publicly accessible on its website with the restrictions suggested and the date of publication.
- The interested parties can submit their comments on the dossiers and suggested restriction together with socioeconomic analysis or any other information studying the advantages and drawback of these restrictions within 6 months of the date of publication.
- The Committee for Risk Assessment shall check and render its opinion if the suggested restrictions are necessary to reduce the risk to human health or environment within 9 months considering the Member State dossier, the dossier prepared by the Agency, and the views of the interested parties (Article 70).

- The Committee for Socioeconomic Analysis shall come to an opinion on the suggested restrictions after studying the dossier and the socioeconomic impact within 12 months of publication. This opinion has to be published on the website by the Agency and invite comments from interested parties within 60 days of the opinion publication.
- The Committee shall adopt its opinion considering comments received. If the opinion of the Committee for Risk Assessment deviates from the restrictions suggested, the deadline for delivering opinion of the Socioeconomic Analysis Committee can be postponed by 90 days (Article 71).

Submission of an Opinion to the Commission

- The submission of an opinion to the Commission is as per Article 72 of this regulation. The opinions of the Committees of Risk Assessment and Socioeconomic Analysis shall be submitted to the Commission by the Agency on the restriction suggestions with documents and evidence submitted upon request. If either of the Committee is not able to come to an opinion by the deadline, then the Agency shall inform the Commission with proper reasons. The opinions of the Committees shall be published on the website by the Agency without delay.

Commission Decision

- Article 73 covers the decision made by the Commission. The Commission shall prepare a draft amendment to Annex XVII once Article 68 conditions. It shall be fulfilled either 3 months after obtaining the opinion or before the deadline set in Article 71 if the Committee has not come to an opinion.
- The Commission shall provide a detailed report with explanation for the difference when the amendment differs from the original proposal or the opinion of the Agency is boycotted. The Commission is assisted by an advisory committee composed of the representatives of the Member States and chaired by the representative of the Commission. This representative has to submit a draft of measures to be taken to the Committee, and the decision has to be taken within a time limit based on the urgency based on the evidence presented and may be through a voting system [21]. The draft amendment shall be submitted to the Member States by the Commission 45 days before the voting.

6 Reach Safety Data Sheet [1]

The supplier of a substance or a preparation shall provide the recipient of the substance or preparation with a safety data sheet complied in accordance with Annex II where (i) a substance or preparation meets the criteria for classification as

dangerous (Directives 67/548/EEC or 1999/45/EC) or (ii) substance is persistent, bioaccumulative, and toxic or very persistent and very bioaccumulative in accordance with the criteria set out in Annex XIII or (c) a substance is included in the list established in accordance with Article 59(1) for other reasons. The safety data sheet might not be supplied for dangerous substances or preparations sold to general public if sufficient information and measures necessary for protection of human health, safety, and environment are available to users. However, the supplier shall provide the safety data sheet (electronic copy or free of cost) at request by the recipient in accordance with Annex II.

The safety data sheet shall be supplied in an official language of the Member State(s), where the substance or preparation is placed on market, and shall contain the following information:

(i) Identification of the substance/preparation and of the company/undertaking.
(ii) Hazards identification.
(iii) Composition/information on ingredients.
(iv) First-aid measures.
(v) Fire-fighting measures.
(vi) Accidental release measures.
(vii) Handling and storage.
(viii) Exposure controls/personal protection.
(ix) Physical and chemical properties.
(x) Stability and reactivity.
(xi) Toxicological information.
(xii) Ecological information.
(xiii) Disposal considerations.
(xiv) Transport information.
(xv) Regulatory information.
(xvi) Other information.

Any downstream user shall include relevant exposure scenarios and use other relevant information, from the safety data sheet supplied to him when compiling his own safety data sheet for identified uses. The suppliers shall update the safety data sheet without delay if:

(i) New information which may affect the risk management measures or new information on hazards becomes available.
(ii) Once an authorization has been granted or refused.
(iii) Once a restriction has been imposed.

The new, dated version of the information, identified as “Revision: (date),” shall be provided by the supplier to all former recipients, who have been supplied with the substance or preparations within the preceding 12 months.

Bibliography

1. legislation.gov.uk - Regulation (EC) No 1907/2006 of the European Parliament and of the Council. 18 Dec. 2006, https://eur-lex.europa.eu/legalcontent/EN/TXT/PDF/?uri=CELEX:32006R1907&from=EN. Accessed 12 Apr. 2020
2. Chemsafetypro, https://www.chemsafetypro.com/Topics/EU/REACH_Regulation_EC_No_1907_2006.html. Accessed 4 Jun. 2020
3. OJ L 183, 29.6.1989, p. 1. Directive as amended by Regulation (EC) No 1882/2003.
4. OJ L 257, 10.10.1996, p. 26. Directive as last amended by Regulation (EC) No 166/2006 of the European Parliament and of the Council (OJ L 33, 4.2.2006, p. 1).
5. OJ L 327, 22.12.2000, p. 1. Directive as amended by Decision No 2455/2001/EC of the European Parliament and of the Council (OJ L 331, 15.12.2001, p. 1).
6. OJ L 311, 28.11.2001, p. 1. Directive as last amended by Directive 2004/28/EC of the European Parliament and of the Council (OJ L 136, 30.4.2004, p. 58).
7. OJ L 311, 28.11.2001, p. 67. Directive as last amended by Directive 2004/27/EC of the European Parliament and of the Council (OJ L 136, 30.4.2004, p. 34).
8. OJ L 40, 11.2.1989, p. 27. Directive as last amended by Regulation (EC) No 1882/2003.
9. OJ L 184, 15.7.1988, p. 61. Directive as last amended by Regulation (EC) No 1882/2003.
10. OJ L 84, 27.3.1999, p. 1. Decision as last amended by Decision 2004/357/EC (OJ L 113, 20.4.2004, p. 28).
11. OJ L 268, 18.10.2003, p. 29. Regulation as amended by Commission Regulation (EC) No 378/2005 (OJ L 59, 5.3.2005, p. 8).
12. OJ L 213, 21.7.1982, p. 8. Directive as last amended by Commission Directive 2004/116/EC (OJ L 379, 24.12.2004, p. 81)
13. Council Directive 91/414/EEC of 15 July 1991 concerning the placing of plant protection products on the market.
14. Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing of biocidal products on the market.
15. Directive 98/70/EC of the European Parliament and of the Council of 13 October 1998 relating to the quality of petrol and diesel fuels.
16. Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products.
17. Regulation (EC) No 1935/2004 of the European Parliament and of the Council of 27 October 2004 on materials and articles intended to come into contact with food and repealing Directives 80/590/EEC and 89/109/EEC.
18. Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations.
19. Annex I to Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.
20. Council Directive 67/548/EEC of 27 June 1967 on the approximation of laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances.
21. Article 133(4) of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC and COUNCIL DECISION laying down the procedures for the exercise of implementing powers conferred on the Commission (1999/468/EC).

22. Section 2 of Annex VI of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.
23. Section 6.4 of Annex I, of Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.
24. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.
25. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
26. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.
27. Council Directive 96/61/EC of 24 September 1996 concerning integrated pollution prevention and control
28. Article 4(1) of Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy.
29. Regulation (EC) No 850/2004 of the European Parliament and of the Council of 29 April 2004 on persistent organic pollutants.
30. Article 11(3)(g) of Directive 2000/60/EC of the European Parliament and of the Council of 23 October 2000 establishing a framework for Community action in the field of water policy and legislation adopted under Article 16 of the same Directive.

EU 1272/2008 – Classification, Labelling and Packaging of Substances and Mixtures

Indumathy Jagadeeswaran and Harini Sriram

1 Introduction

I. *EU and EC 1272/2008*

The European Parliament and the Council of the European Union with respect to the treaty establishing the European Community, Article 95, the Commission's proposal, the European Economic and Social Committee's opinion, procedures laid down in Article 251 of the Treaty and European Commission (EC) lays down regulations for ensuring the safety of the patient. These regulations were split into different sections in order to provide a detailed description about the specific categories and chemical used in the medical devices.

One such regulation is EU CLP Regulation (EC) No 1272/2008. CLP stands for Classification, Labelling, and Packaging of substances and mixtures. For appropriate classification and labelling of chemicals, CLP introduced the United Nations Globally Harmonized Systems (UN GHS) into Europe on 20 January 2009. Initially, there exist different systems for classification and labelling of chemicals around the world, which led to a huge confusion, misunderstandings among workers, potential errors, and dissatisfaction of consumers. The major cause of the insufficiency is different countries using differing forms of labeling and safety data sheets. Hence, UN has come forward to develop a globally harmonized system of classification and labeling of chemicals, known as GHS. In the initial stage, GHS bound to Europe non-legally as an international agreement; later CLP introduced GHS into Europe [1].

I. Jagadeeswaran (✉)
Department of Biological Sciences, Southern Methodist University, Dallas, TX, USA

H. Sriram
National Dental Centre Singapore, Singapore, Singapore

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_14

II. *Establishment of Compliance with CLP Regulation*

The Article 46 of the CLP Regulation on Enforcement and Reporting circumstances that the "Member States shall take all necessary measures, including maintaining a system of official controls, to ensure that substances and mixtures are not placed on the market, unless they have been classified, labelled, notified and packaged in accordance with this Regulation." Companies need to classify the substances or mixtures, and C&L notifications will be submitted to ECHA (European Chemical Agency). Subsequently labelling and packaging of their products was done in accordance with the CLP regulation. Information about CLP classification and labelling will be located in the CLP complaint Safety Data Sheet. The following information was prepared and communicated with the downstream users for the compliance [2]:

– Classification
– Labelling and packaging
– C&L notification
– Safety data sheet

III. *Purpose and Scope* [3]

The primary strategy of the regulation is to ensure safety of human health and environment and movement of substances, mixtures, and articles as specified in Article 4(8):

(a) Harmonizing the criteria and/or strategy of substances and mixtures classification and the establishment of rules on labelling and packaging for hazardous substances and mixtures.
(b) Providing an obligation for:
    – Classification of substances and mixtures placed on the market by manufacturers, importers, and downstream users
    – Labelling and packaging of substances and mixtures placed on the market by suppliers
    – Classification of those substances not placed on the market which must undergo registration or notification under Regulation (EC) No 1907/2006 by manufacturers, producers of articles, and importers
(c) An obligation will be ascertained to the manufacturers and importers of substances for notifying the agency of such specific classifications and label elements, if they have not been submitted to the agency as part of a registration under Regulation (EC) No 1907/2006.
(d) Establishment of a list of substances with their harmonized classifications and labeling elements at community level in Part 3 of Annex VI.
(e) Inventory substances classification and labelling made up of all notifications, submissions, and harmonized classifications and labeling elements as referred to in points (c) and (d).

This regulation does not apply to the following:

(a) Radioactive substances and mixtures that are in the scope of Council Directive 96/29/Euratom of 13 May 1996 which has laid down the primary safety standards for the protection of workers' health. It also takes public health into account ensuring against danger arising from ionizing radiation.
(b) Substances and mixtures that are in subject to customs supervision which do not undergo any treatment or processing, which are in temporary storage or in a free zone or free warehouse with a re-exportation or in transit view.
(c) Non-isolated intermediates.
(d) Substances and mixtures that are used in scientific research and development, which are not placed in the market and provided to be used under specific and controlled conditions in accordance with Community workplace and environmental legislation.

- As defined in Directive 2006/12/EC of the European Parliament and Council of 5 April 2006 on waste, it is not a substance, mixture, or article within the meaning of Article 2 of this Regulation.
- In specific cases where, the substances or mixtures are of interest to the defense, the member states may allow for exemptions from this regulation.
- The regulation is not applicable to substances and mixtures in the following form which are in finished state intended for the final user.
- Medicinal products as defined in Directive 2001/83/EC.
- Veterinary medicinal products as defined in Directive 2001/82/EC.
- Cosmetic products as defined in Directive 76/768/EEC.
- Medical devices as defined in Directives 90/385/EEC and 93/42/EEC, which are invasive or used in direct physical contact with the human body and in Directive 98/79/EC.
- Food or feeding stuffs as defined in Regulation (EC) No 178/2002 including when they are used as a food additive (89/107/EEC), flavoring (Directive 88/388/EEC and Decision 1999/217/EC), additive (Regulation (EC) No 1831/2003), or animal nutrition (Directive 82/471/EEC) in foodstuffs or feeding stuffs within the scope of these Directives.
- The regulation shall not apply to dangerous goods by air, road, sea, rail, or inland waterways transportation.

IV. *Hazardous Substances and Mixtures and Specification of Hazard Classes* [4]

A hazardous substance is a mixture which can fulfill the criteria relating to physical hazards, health hazards, or environmental hazards which has been laid down in Parts 2 to 5 of Annex I [5]. It can be classified in relation to the respective hazard classes specified in Annex I. The substances or mixtures were classified based on the route of exposure or nature of effects.

V. *General Obligations to Classify Label and Package*

Substances placed on market shall be classified based on various stakeholders (manufacturers, producers of articles, and importers) involved, and users shall

classify substances or mixtures in accordance with Title II (discussed in Sect. 2 of this chapter). Without prejudice to the requirements of paragraph 1 (discussed in paragraph I, Sect. 2 of this chapter), manufacturers, producers of articles and importers shall classify those substances not placed on the market in accordance with Title II. In cases where substances are subject to harmonized classification and labelling in accordance with Title V (discussed in Sect. 2 of this chapter) through an entry in Part 3 of Annex VI, Title II shall not be performed in that entry. However, where the substance also falls within one or more hazard classes or differentiations, Title II shall be carried out for those hazard classes or differentiation with packaging in accordance with Titles III (discussed in Sect. 3 of this chapter) and IV (discussed in Sect. 4 of this chapter). The regulation also states that distributors may use the classification for a substance or mixture derived in accordance with Title II. A mixture referred to in Part 2 of Annex II that contains any substance classified as hazardous shall not be placed on the market, unless it is labelled in accordance with Title III.

2 Classification

I. *Identification and Examination of Available Information* [4–6]

The stakeholders (manufacturers, importers, and downstream users) of a substance or a mixture shall identify whether the substance or a mixture entails a physical, health, or environmental hazard, based on the relevant criteria laid down in Parts 2 to 5 of Annex I [5] of EU 1272-2008, in particular:

(a) The data generated with any of the test methods referred to in Article 13(3) of Regulation (EC) No 1907/2006
(b) Internationally recognized sound scientific principles or procedures
(c) Data from epidemiological, occupational, or accident databases
(d) Any other information in Section 1 of Annex XI to Regulation (EC) No 1907/2006
(e) Any new scientific or any other information generated under internationally recognized chemical programs

The information shall relate to forms or physical states in which the substance or mixture is placed on market or expected to be used. If there is no information or no adequate data in the existing database, then the stakeholder shall use other available information on individual substance or similar tested mixtures to determine their hazardousness. However, the manufacturer, importer, or downstream user should ascertain that information is adequate and reliable for the purpose of the evaluation pursuant to Article 9(4) of this regulation.

A. *Generating New Information for Substances and Mixtures* [7]

If the information on the substance or mixture in not available in Annex I of EU 1272-2008 regulation and the manufacturer, importer, or downstream user has

exhausted all other means of generating information including by applying the rules provided for in Section 1 of Annex XI to Regulation (EC) No 1907/ 2006, new tests may be performed in accordance to Article 9 of this regulation, to determine whether the substance or a mixture entails a physical, health, or environmental hazard. The tests shall be conducted in accordance with article 8(3) of this regulation [3] with one of the following methods:

(a) The data generated with any of the test methods referred to in Article 13(3) of Regulation (EC) No 1907/2006
(b) Internationally recognized sound scientific principles or procedures

Tests on animals for generating new data for this regulation, within the meaning of Directive 86/ 609/EEC, shall be undertaken only where no other alternatives are possible [8]. Furthermore, tests on non-human primates and humans shall also be prohibited for the purposes of this Regulation. However, data obtained from other sources including clinical studies can be used. The new tests shall be carried out in the forms or physical states in which the substance or mixture is placed on market or expected to be used. For example, possible methods for determining flash point of flammable liquids are cited below:

Methods for determining the flash point of flammable liquids [6]	
European standards:	EN ISO 1516 as amended Determination of flash/no flash – Closed cup equilibrium method
	EN ISO 1523 as amended Determination of flash point – Closed cup equilibrium method
	EN ISO 2719 as amended Determination of flash point – Pensky-Martens closed cup method
	EN ISO 3679 as amended Determination of flash point – Rapid equilibrium closed cup method
	EN ISO 3680 as amended Determination of flash/no flash – Rapid equilibrium closed cup method
	EN ISO 13736 as amended Petroleum products and other liquids – Determination of flash point – Abel closed cup method
National standards:	
Association française de normalisation, AFNOR:	NF M07-036 as amended Détermination du point d'éclair – Vase clos Abel-Pensky (identical to DIN 51755)
British Standards Institute	BS 2000 Part 170 as amended (identical to EN ISO 13736)

Methods for determining the flash point of flammable liquids [6]	
Deutsches Institut für Normung	DIN 51755 (flash points below 65 C) as amended Prüfung von Mineralölen und anderen brennbaren Flüssigkeiten; Bestimmung des Flammpunktes im geschlossenen Tiegel, nach Abel-Pensky (identical to NF M07-036)

Source: Table 2.6.3, Annex I [5]; Methods for determining the flash point of flammable liquids; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

II. *Evaluation of Hazard Information and Decision on Classification*

A. *Evaluation of Hazard Information* [9]

The stakeholder users of a substance or a mixture shall evaluate the information identified in accordance with Sect. 2 of this chapter by each hazard class or differentiation in Parts 2 to 5 of Annex I [5], to ascertain the hazards. In evaluating available test data for a substance or a mixture, other than those referred to in Article 8(3), the stakeholder users shall compare the test methods employed with that Article in order to determine whether those test methods affect the evaluation referred to in paragraph I, Sect. 2 of this Article. When the criteria cannot be applied directly to available identified information then the stakeholders shall carry out an evaluation by applying a weight of evidence determination using expert judgement in accordance with section 1.1.1 of Annex I [5] to this Regulation, weighing all available information having a bearing on the determination of the hazards of the substance or the mixture, and in accordance with section 1.2 of Annex XI to Regulation (EC) No 1907/2006 [10].

When Article 6(5) is available, stakeholders shall apply the bridging principles referred to in Section 1.1.3 and in each section of Parts 3 and 4 of Annex I [5] for the purpose of evaluation. However, where information permits the application neither of the bridging principles nor the principles for using expert judgement as described in Part 1 of Annex I, stakeholders shall evaluate the information by each section of Parts 3 and 4 of Annex I [5]. While evaluating the information, physical states in which the substances or mixtures are marketed shall be used by the stakeholders.

B. *Concentration Limits and M-Factors for Classification of Substances and Mixtures* [11]

Specific concentration limits and generic concentration limits are limits assigned to a substance indicting a threshold at or above which the presence of that substance in another substance or mixture is identified as impurity, additive, or individual constituent leading to classification of the substance or mixture as hazardous [4]. Stakeholders shall set specific concentration limits where adequate, and reliable

scientific information shows that the hazard of a substance is evident at a level below concentrations set for any hazard class in either specific concentration limits (part 2 of Annex I) or generic concentration limits (Parts 3, 4 and 5 of that Annex I). In exceptional circumstances, stakeholders shall set specific concentration limits where a hazard of a substance classified as hazardous is not evident at a level above the concentrations set for the relevant hazard class in Part 2 of Annex I or above the generic concentration limits set for the relevant hazard class in Parts 3, 4, and 5 of that Annex I.

M-factors for substances classified as hazardous to the aquatic environment acute category 1 or chronic category shall be established by stakeholders. M-factors and specific concentration limits shall not be set for harmonized hazard classes or differentiations for substances included in Part 3 of Annex VI, for which an M-factor is given in Part 3. However, where an M-factor is not given in Part 3 for hazardous substances to the aquatic environment, an M-factor based on available data for the substance shall be set by the stakeholder. When a mixture including the substance is classified by the stakeholder using the summation method, this M-factor shall be used. In setting the specific concentration limit or M-factor, stakeholders shall consider any specific concentration limits or M-factor limits for that substance which have been included in the classification and labelling inventory. Such specific concentration limits set shall take precedence over the concentrations in the relevant sections of Part 2 of Annex I or the generic concentration limits for classification sections of Parts 3, 4, and 5 of Annex I.

C. *Cutoff Values* [12]

Cutoff values indicate when the presence of a substance needs to be taken into account for the purposes of classification of a substance or a mixture containing that hazardous substance, whether as an identified impurity, additive, or individual constituent. When a substance or a mixture inherently classified as hazardous, either in the form of an identified impurity, additive, or individual constituent, this shall also be taken for classification, if the concentration of identified impurity, additive or individual constituent is equal to, or greater than, the applicable cut-off value in accordance with section 1.1.2.2 of Annex I.

Hazard class	Generic cutoff values to be taken into account
Acute toxicity:	
Category 1–3	0.1%
Category 4	1%
Skin corrosion/irritation	1%
Serious damage to eyes/eye irritation	1%
Hazardous to aquatic environment	
Acute Category 1	0.1%
Chronic Category 1	0.1%
Chronic Category 2–4	1%

Source: Table 1.1.2.2, Annex I [5]; Cut-off values; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

D. *Specific Cases Requiring Further Evaluation* [13]

As a result of the evaluation as per Article 9 of this regulation, the following properties or effects are identified in accordance to Article 12 of this regulation, which the stakeholder users shall take them into account for the purpose of classification:

(a) Adequate and reliable information shows that in practice the physical hazards of a substance or a mixture differ from those shown by tests.
(b) Conclusive scientific experimental data show that the substance or mixture is not biologically available and those data have been ascertained to be adequate and reliable.
(c) Adequate and reliable scientific information demonstrates the potential occurrence of synergistic or antagonistic effects among the substances in a mixture.

E. *Decision to Classify Substances and Mixtures* [14]

If the evaluation as per Article 9 and Article 12 shows that the hazards associated with the substance or mixture meet the criteria for classification in one or more hazard classes or differentiations in Parts 2 to 5 of Annex I, stakeholders shall classify the substance or mixture in relation to the relevant hazard class or classes or differentiations by assigning the following:

(a) One or more hazard categories for each hazard class or differentiation
(b) Subject to Article 21, one or more hazard statements corresponding to each hazard category assigned in accordance with (a)

For example, a flammable liquid shall be classified in one of the three categories for this class in accordance with Annex I.

Category	Criteria for flammable liquids
1	Flash point < 23 °C and initial boiling point ≤ 35 °C
2	Flash point < 23 °C and initial boiling point > 35 °C
3	Flash point ≥ 23 °C and ≤ 60 °C (1)
(1) For the purpose of this Regulation, gas oils, diesel, and light heating oils having a flash point between ≥ 55 °C and ≤ 75 °C may be regarded as Category 3	

Source: Table 2.6.1, Part 2 of Annex I [5]; Criteria for flammable liquids; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

F. *Specific Rules for the Classification of Mixtures* [15]

The classification of a mixture shall not be affected where the evaluation of the information indicates any of the following:

(a) Substances in the mixture react slowly with oxygen, carbon dioxide, water vapor and other substances in the mixture to form different substances at low concentration.
(b) Substances in the mixture may self-polymerize to form oligomers or polymers, at low concentration.

A mixture need not be classified for explosive, oxidizing, or flammable properties as referred to in Part 2 of Annex I if any of the following requirements are met:

(a) None of the substances in the mixture possess any of those properties, and the mixture is unlikely to present hazards of such kind.
(b) In the event of a change in the composition of a mixture, scientific evidence indicates that it will not lead to a change in classification.
(c) Where a mixture is placed on the market in the form of an aerosol dispenser, it satisfies Article 8(1a) of Council Directive 75/324/EEC of 20 May 1975 on the approximation of the laws of the Member States relating to aerosol dispensers.

G. *Review of Classification for Substances and Mixtures* [16]

The stakeholders shall take all reasonable steps available to them to make themselves aware of new scientific or technical information that may affect the classification. When stakeholder becomes aware of such information which he considers to be adequate and reliable, that stakeholder shall carry out evaluation in accordance with this chapter. The stakeholder manufacturer, importer, or downstream user introduces a change to a mixture that has been classified as hazardous, and that stakeholder shall carry out a new evaluation in accordance with this chapter where the change is as follows:

– A change in the composition of the initial concentration of one or more of the hazardous constituents in concentrations at or above the limits in Table 1.2 of Part 1 of Annex I.
– A change in the composition involving the substitution or addition of one or more constituents in concentrations at or above the cutoff value referred to in Article 11(3).
– A new evaluation in accordance with paragraphs 1 and 2 shall not be required if there is valid scientific justification that this will not result in a change of classification.

The stakeholder shall adapt the classification with the results of the new evaluation except where there are harmonized hazard classes or differentiations for substances included in Part 3 of Annex VI. 5. For paragraphs 1 to 4 of Article 15 of this regulation, when the substance or mixture concerned is within the scope of Directive 91/414/EEC or Directive 98/8/EC, the requirements of those Directives shall also apply.

H. *Classification of Substances Included in the Classification and Labelling Inventory* [17]

Manufacturers and importers may classify a substance differently from the classification already included in the classification and labelling inventory, provided they submit the reasons for the classification to the Agency together with the notification in accordance with Article 40. 2. Paragraph 1 shall not apply if the classification included in the classification and labelling inventory is a harmonized classification included in Part 3 of Annex VI [18].

3 Labelling

In accordance with Article 17 of the CLP regulation [19], a hazardous substance contained in a packaging is required to bear a label with the name, address, and telephone number of the supplier(s), the nominal quantity of the substance/mixture in the package unless specified elsewhere other than the label, product identifiers (Article 18), hazard pictograms (Article 19), signal words (Article 20), hazard statements (Article 21), precautionary statements (Article 22), and supplemental information (Article 25). Each of these elements follows the guidelines given under Articles 18–25 which will be discussed in brief here. The labels are written in the official language(s) of the Member of State where the substance/mixture is marketed. The labels can bear more languages than those required provided all the languages hold the same details.

A. *Product identifiers* [20] are defined as the term used for the identification of the substance/mixture as given in Article 31 of the Regulation (EC) No 1907/2006 (also known as the safety data sheet) without any prejudice with Article 17(2). Substances and mixtures are identified in the label by different guidelines. Each substance is given an index number, EC number, CAS number, and International Chemical Identifications. Impurities and additives are not usually mentioned unless they contribute significantly to the classification. The substances are named and designated identification number as included in Table 3.1 in Part 3 of Annex VI, and for those not included, name and identification number are given as per classification and labelling inventory. A substance neither in Part 3 of Annex VI nor the classification and labelling inventory is identified by number provided by the Chemical Abstracts Service (CAS no.) along with its IUPAC nomenclature or international chemical name(s). In case of non-availability of CAS no., only the IUPAC nomenclature or international chemical name(s) is used. When the given IUPAC nomenclature exceeds 100 characters, then usually the name, trade name, or abbreviation is used as referred to in Section 2.1.2 of Annex VI in accordance with Article 40. A product identifier for ethanol is cited for example as below:

Index no	International chemical identification	EC no	CAS no
603-002-00-5	Ethanol; ethyl alcohol	200-578-6	64-17-5

Source: Table 3.1, Part 3 of Annex VI [18]; Product identifier for ethanol; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

The product identifier for mixtures must include trade name or the designation of the mixture along with identity of all the substances in the mixture that are responsible for major health hazards such as acute toxicity, skin corrosion/irritation, serious eye damage/irritation, respiratory or skin sensitization, germ cell mutagenicity, carcinogenicity, reproductive toxicity, and specific target organ toxicity with single and repeated exposure and aspiration hazard. A maximum of four chemical names can be given considering the major health hazards associated unless more are needed depending on the severity of the hazards.

B. *Hazard pictogram(s)* [21] convey a very important and specific information about the hazard involved in a pictorial form. With the help of Table 1 in Annex I, the pictograms are provided with the label elements for each hazard class with rules for labelling of packaging (Article 33) which will be discussed in the packaging section of the chapter. Hazard pictograms are square in shape set at a point and have a black symbol in a white background framed with a red frame. They must be 1/15th of the surface area of the harmonized label with a minimum area not less than 1cm [2]. The dimensions of the pictogram on labels depend on the capacity of the package. For packages not exceeding 3 L, the pictogram must be at least 52mm × 74mm, greater than 3 L and less than 50 L holds a pictogram of at least 74mm × 105mm, greater than 50 L and less than 500 L holds a pictogram of at least 105mm × 148mm, and for packages more than 500 L, the pictogram must be 148mm × 210mm. An example of a pictogram assigned for flammable substances/mixtures from Annex V is given below:

Pictogram (1)	Hazard class and hazard category (2)
 GHS02	Section 2.2 Flammable gases, hazard category 1 Section 2.3 Flammable aerosols, hazard categories 1, 2 Section 2.6 Flammable liquids, hazard categories 1, 2, 3 Section 2.7 Flammable solids, hazard categories 1, 2 Section 2.8 Self-reactive substances and mixtures, Types B, C, D, E, F Section 2.9 Pyrophoric liquids, hazard category 1 Section 2.10 Pyrophoric solids, hazard category 1 Section 2.11 Self-heating substances and mixtures, hazard categories 1, 2 Section 2.12 Substances and mixtures, which in contact with water, emit flammable gases, hazard categories 1, 2, 3 Section 2.15 Organic peroxides, Types B, C, D, E, F

Source: Table 1.2, Annex V [22]; Hazard pictogram for symbol: Flame; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

Most of the time, more than one pictogram may be needed to be used. Article 26 provides the principles of precedence of hazard pictograms. When required to use more than one pictogram for the same hazard class, the hazard pictogram corresponding to the most severe hazard category for each hazard class is to be included. Where "GHS01: exploding bomb" for explosives applies "GHS02: flame" for flammable and "GHS03: flame over circle" for oxidizing substances is optional unless it is compulsory to use more than one pictogram. Similarly, if "GHS06: skull and cross bones" for acute toxicity applies, then "GHS07: exclamation mark" for skin and eye irritation need not be given. If the pictogram "GHS05: corrosion" for skin corrosion or eye damage is applicable, "GHS07" need not be included. Wherever "GHS08: health hazard" applies for respiratory sensitization, the hazard pictogram "GHS07" shall not apply.

C. *Signal word* [23] refers to the level of severity of the potential hazard of the substance/mixture included in the package. The signal words are "Danger" or "Warning." The signal words are assigned for each specific classification and for each hazard class as included in Parts 2–5 of Annex I. This holds information such as definition, hazard classification criteria, hazard category, hazard communication, and additional classification consideration for all the hazard classes.

The signal word appropriate for the particular substance/mixture categorized by the classification criteria is to be used. For example, for flammable liquids, the criteria for assigning signal word are based on the flash point of the liquid. For liquids whose flash point is < 23 °C and initial boiling point ≤ 35 °C comes under Category 1, Category 2 consists of liquids with flash point < 23 °C and initial boiling point > 35 °C and under Category 3 liquids of flash point ≥ 23 °C and ≤ 60 °C. The signal word for Category 1 and 2 is "Danger" and for Category 3 is "Warning." It should be noted that both the signal words cannot be used on the same label.

D. *Hazard statements* [24] are assigned to describe the nature of the hazards associated with the substance/mixture including the degree of hazard often indicated by H followed by a 3-digit code like "H224." The hazard statements are given in Annex III [25] in all the official European languages for all the physical, health, and environmental hazards. Like the other label elements, hazard statements are included in Parts 2–5 of Annex I provided based on the hazard classification criteria of the substance/mixture. To quote an example, flammable liquids of Category 1 (described in previous section), the hazard statement "H224: Extremely flammable liquid and vapor" is given. Category 2 and Category 3 flammable liquids have to bear "H225: Highly flammable liquid and vapor" and "H226: Flammable liquid and vapor" in the label, respectively. In addition to the hazard statements included in Annex III, new set of 3-digit codes are designated to certain hazard statements for substances included in Part 3 of Annex VI [26] and to be used together with hazard statements mentioned previously. As per "Article 27: Principles of precedence of hazard statements," if a substance/mixture has several hazards associated with it, then all hazard statements pertaining to all the different hazards classes should appear on the label unless the statements are repetitive. Propan-1-ol belongs to category 2 flammable liquid which causes serious eye damage/eye irritation and specific organ toxicity after single exposure. Hence, the package of propan-1-ol will hold a label with all three hazard statements "H225: Highly flammable liquid and vapor," "H318: Causes serious eye damage," and "H336: May cause drowsiness or dizziness."

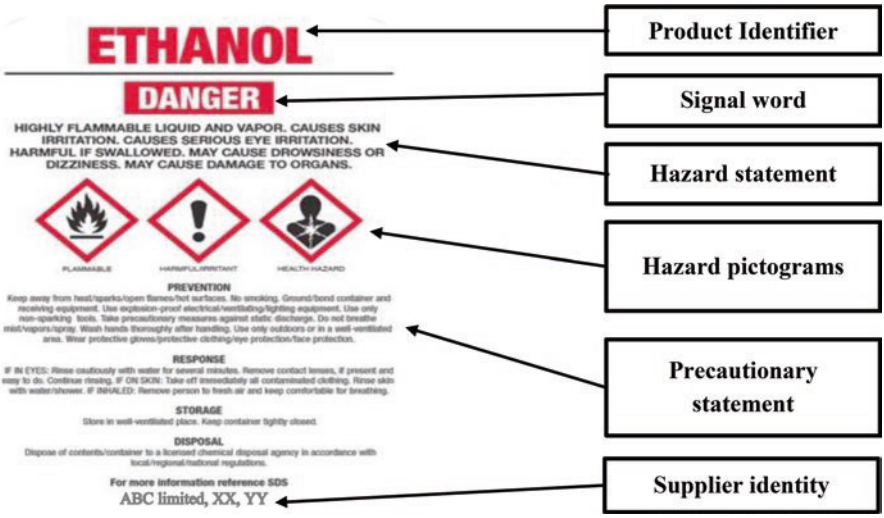
E. *Precautionary statements* [27] are phrases that recommend measure(s) to mitigate/avoid adverse effects after exposure to hazardous substance/mixture through usage or disposal. Similar to hazard statements, precautionary statements have letter "P" followed by 3-digit code assigned for different hazard class and category. The criteria for selection of precautionary statements are given in Part 1 of Annex IV [26]. The actual statements are given under Part 2 of Annex IV in all the official European languages. The statements are provided in tables in Parts 2–5 of Annex I [5] along with other label elements. There are different precautionary statements for general usage, prevention, response, storage, and disposal. For flammable liquids, prevention precautionary statement will state "P210: Keep away from heat/ sparks/open flames/hot surfaces. No smoking." Response precautionary statement will state "P303: If on skin (or hair)," "P353: Rinse skin with water/shower," "P361: Remove/Take off immediately all contaminated clothing," and "P370+378: In case of fire: Use for

extinction." Storage precautionary statement will state "P403+235: Store in a well-ventilated place. Keep Cool." Disposal precautionary statement will state "P501: Dispose of contents/container to." As per Article 28 [28] of principles of precedence of precautionary statements, not more than six precautionary statements should appear on the label unless necessary to communicate the severity of the hazard. When a substance/mixture is supplied to the general public, a precautionary statement for the disposal of the substance/mixture as well as the packaging should appear on the label. In cases where disposal of the substance/mixture and the package does not produce any hazard to human health or the environment, no disposal precautionary statement is required. Some statements shall be omitted if they are redundant or unnecessary for the substance/mixture or packaging.

Classification	Category 1	Category 2	Category 3
GHS pictograms			
Signal word	Danger	Danger	Warning
Hazard statement	H224: Extremely flammable liquid and vapor	H225: Highly flammable liquid and vapor	H226: Flammable liquid and vapor
Precautionary statement prevention	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280	P210 P233 P240 P241 P242 P243 P280
Precautionary statement response	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378	P303 + P361 + P353 P370 + P378
Precautionary statement storage	P403 + P235	P403 + P235	P403 + P235
Precautionary statement disposal	P501	P501	P501

Source: Table 2.6.2, Annex I [5]; label elements for flammable liquids; CLP regulation (EC) no 1272/2008 of the European Parliament and of the Council of 16 December 2008

F. *Supplemental information* [29] should be included in the label for substances/mixtures for their physical, health, or environmental hazards involved. Statements to be included are given in Sections 1.1 and 1.2 of Annex II [30] and Part 2 of Annex III [25]. For substances/mixtures not classified as flammable but may form flammable/explosive vapor-air mixtures such as halogenated hydrocarbons and mixtures containing volatile flammable component or mixtures that lose volatile non-flammable component, a supplemental hazard statement should say "EUH018: In use, may form flammable/explosive vapor-air mixture." For substances in Part 3 of Annex VI [31], supplemental hazard statements are given as in Table 3.1. Lithium is given with "EUH014: 'Reacts violently with water" supplemental hazard statement. Special supplemental statement is to be included for plant protection products in accordance with Annex V [32] of Directive 91/414/EEC, "EUH401: To avoid risks to human health and the environment, comply with instructions for use." The suppliers can include supplemental statements apart from those mentioned above provided it does not contradict or cast doubt on and make it more difficult to identify the label elements. Statements that are inconsistent with the classification of substance/mixture such as "non-toxic," "non-harmful," and "ecological" should not appear on the label or the packaging of substance/mixture. The hazard pictograms of the substances/mixtures classified as hazard to ozone layer shall not be included in the label. Signal words, hazard statements, and precautionary statements are to be included in the supplemental information section of the label. Mixtures containing lead, cyanoacrylates, cements, isocyanates, epoxy constituents with an average molecular weight ≤ 700, active chlorine, cadmium (alloys) used in brazing/soldering, at least one sensitizing substance, halogenated hydrocarbons, and mixtures not intended for general public use have supplemental statements derived from Part 3 of Annex III along with the product identifier and the name and address of the supplier. To quote an example, mixtures containing lead will have supplemental information "EUH201/201A: Contains lead. Should not be used on surfaces liable to be chewed or sucked by children. Warning! Contains lead" given in the label. A sample labeling (core labelling elements) for flammable liquid ethanol is cited below:



G. *Derogations from labelling requirements for special cases* [33] are laid down under Section 1.3 of Annex I [5] which apply for transportable gas cylinders; gas containers intended for propane, butane, or liquefied petroleum gas; aerosols and containers fitted with a sealed spray attachment and with substances or mixtures classified as presenting an aspiration hazard, metals in massive form, alloys, mixtures containing polymers, mixtures containing elastomers, and explosives on the market or those with pyrotechnic effect. A model derogation for gas cylinders with a water capacity of less than or equal to 150 L would be that the label can bear the generic name or industrial or commercial name of the substance/mixture provided the hazardous substances/mixtures are shown in the body of the cylinder in a legible way.

H. *Exemptions from labelling and packaging requirements* [34] apply to few packaging of smaller sizes. Article 29 provides the guidelines to follow in such cases. In packages of substances/mixtures that are so small to meet the requirements of the label in languages of Member of the State where they are to be marketed, the label elements can be provided in fold-out labels, on tie-on tags, or on an outer packaging. The label should bear at least hazard pictograms, product identifier, and name and telephone number of the supplier. According to Section 1.5.2 of Annex I [5], in packages whose contents do not exceed 125 ml, the hazard statements and precautionary statements can be omitted provided the contents of the packaging are classified under one of the following categories: Oxidizing gases of category 1; Gases under pressure; Flammable liquids of category 2 or 3; Flammable solids of category 1 or 2; Self-reactive substances or mixtures Types C to F; Self-heating substances or mixtures of category 2; Substances and mixtures which, in contact with water, emit flammable gases of categories 1, 2, or 3; Oxidizing liquids of category 2 or 3; Oxidizing solids of category 2 or 3; Organic peroxides types C to F; Acute toxicity of category 4 (if the substances or mixtures

are not supplied to the general public); Skin irritation of category 2; Eye irritation of category 2; Specific target organ toxicity, single exposure of category 2 or 3 (if the substance or mixture is not supplied to the general public); Specific target organ toxicity, repeated exposure of category 2 (if the substance or mixture is not supplied to the general public); Hazardous to the aquatic environment, Acute category 1; or Hazardous to the aquatic environment, Chronic category 1 or 2. Small packages of aerosols dispensers can bear a label attached to it with the name and address or trademark of the supplier, the symbol "3" (inverted epsilon) certifying conformity, code markings enabling the filling batch, inscriptions containing the hazard statement and precautionary statement, and the net contents by weight and by volume (as per Directive 75/324/EEC). Precautionary statements can be omitted for substances/mixtures belonging to Flammable gases of category 2, Reproductive toxicity: effects on or via lactation, Hazardous to the aquatic environment – Chronic of category 3 or 4 when they are contained in packages less than 125 ml. The pictogram, hazard statements, and the precautionary statement can be omitted for "corrosive to metal" substance/mixture when the package does not exceed 125 ml. Soluble packaging intended for single use whose volume do not exceed 25 ml is exempted from printing the label elements only if they are classified under the hazard categories mentioned above (Section 1.5.2.1.1 of Annex I [5]). The outer packaging containing the soluble packaging must bear the necessary label elements as cited by Article 17 [19]. When ready mixed cement and concrete in the wet state is supplied to general public without packaging, it must be accompanied with a copy of the label elements. Exemptions and provisions for certain mixtures that are classified as hazardous to the environment are defined under Part 2 of Annex II [30]. These exemptions are to be determined as per Article 53 [35] once it can be proven that there would be reduction in the environmental impact. The label on the packaging of paints and varnishes that contain lead in quantities exceeding 0,15% (weight of lead) to weight of the mixture should have "EUH201: Contains lead. Should not be used on surfaces liable to be chewed or sucked by children." Packages of volume less than 125 ml use "EUH201A – 'Warning! Contains lead."

The label for a substance/mixture has to be updated by the suppliers without undue delay when any change to the classification and labelling occurs with regard to the protection of human health and environment. All other changes apart from those referred before should be updated to the label by the supplier within 18 months. Plant protective products and adjuvants suppliers shall follow Directives 91/414/EEC or 98/8/EC.

I. *Application of Labels: General Rules for Application of Labels* [36]

The label should be attached to one or more surfaces of the package of the substance/mixture in a horizontally readable manner when set down. The hazard pictogram should stand out against the color and presentation of the label. All the label elements should be clear and indelibly marked and legible and easy to read from the

background of the package. The shape, color, and the size of the pictogram are to be as set out in previous "Hazard pictogram" section. A separate label is not required if all the label elements required by Article 17 [19] are shown on the packaging itself.

There are guidelines for *location of information on the label* [37]. The hazard pictograms, signal word, hazard statements, precautionary statements, and supplemental information are to be located in the same location in the label. The order of the hazard statements and precautionary statements shall be decided by the supplier, grouped by language, and placed together on the label. Apart from hazard pictograms, colors shall be used in other areas for special labelling requirements. Label elements provided for in other communities should be placed in the supplemental information section.

J. *Specific Rules for Labelling of Outer Packaging, Inner Packaging, and Single Packaging* [38]: A package containing an outer packaging, an intermediate packaging, and an inner packaging shall be labelled through different regulations. The outer packaging labels follow the rules on the transport of dangerous goods. Hazard pictograms required by this regulation and same as in the rules for the transport of dangerous goods need not be put on the outer packaging. The outer packaging is not required to be labelled if the intermediate or the inner packaging is visible through it. Single packages should be labelled with the rules of transport of dangerous goods as well by the labelling and packaging regulations in this chapter. When the hazard pictograms relate to the same hazard by both regulations, then only the transport of dangerous goods rules apply.

4 Packaging [39]

Packaging should be designed and constructed such that its content cannot leak and also include specific safety devices prescribed. The packaging and fastening material should not be susceptible to damage or form hazardous compounds by its contents. The packaging and fastening must be solid and strong to withhold all the stresses and strains of handling. The packaging should be solid to ensure it will not loosen and fitted with replaceable fastenings to refasten to avoid spilling of its contents. The hazardous substances/mixtures supplied to the public should not be designed in the shape or form that attracts children or mislead customers. They also should not be in the same form or shape as that of packages containing food, animal feed, or medicinal or cosmetic product. These packaging should also satisfy with the requirements of transport of dangerous goods by air, sea, road, rail, or inland waterways. Packaging containing substances/mixture classified for acute toxicity (category 1–3), specific target organ toxicity (single and repeated exposure category 1), and skin corrosion (category 1) being supplied to the general public should be fitted with child-resistant packaging. Packaging of substances/mixtures which possess aspiration hazard with an exception of aerosols or sealed spray attachment container should bear child-resistant fastenings. Substances/mixtures containing

either ≥3% methanol or ≥ 1% dichloromethane supplied to the public must be fitted with child-resistant fastenings. Reclosable packages with child-resistant packaging should follow guidelines of EN ISO standard 8317 adopted by the European Committee for standardization (CEN) and the International Standard Organization (ISO).

Child-resistant fastenings on non-reclosable packages follow CEN standard EN 862. Conformity to these standards should be certified only by laboratories complying with Standard EN ISO/IEC 17025. If the packaging is sufficiently safe that the children cannot access its contents, then the tests assigned by the ISO standards need not be performed. In other cases, a certificate from the ISO-certified laboratory is needed stating the closure does not require a test to be performed or the closure has been tested and found to be efficient. Packaging of any capacity have to be fitted with tactile warning "Danger" when supplied to the general public for containing substances classified for acute toxicity, skin corrosion, germ cell mutagenicity category 2, carcinogenicity category 2, reproductive toxicity category 2, respiratory sensitization, or specific target organ toxicity categories 1 and 2, aspiration hazard, or flammable gases, liquids, and solids in categories 1 and 2. This does not apply to aerosols classified as "extremely flammable aerosols" or "flammable aerosols." The technical specifications for tactical devices should conform with EN ISO standard 11683 "Packaging – Tactile warnings of danger – Requirements."

5 C&L Notification and Inventory

Scope [40] The substances subject to registration according to Regulation (EC) No 1907/2006 [10] and substances classified in Part 3 of Annex VI [31] and to be placed on the market either on its own or as a mixture above the specified concentrations are in scope of this regulation.

Manufacturers or importers (notifier(s) and registrant(s)) who place the substances on the market are obligated to notify the European Chemical Agency (from here on Agency) for the following information to be included in the classification and labelling inventory [41]:

(a) The identity of the notifier who places substances/mixtures on the market such as name, address, telephone number, fax number, e-mail address, contact person, and location of the production site. In case of more than one notifier, the lead notifier's name, address, telephone number, fax number, and e-mail address along with the registration of the other notifiers. The lead notifier should be identified by another notifier by providing his name, address, telephone number, fax number, and e-mail address together with the registration submitted by the lead notifier. When a third party is assigned to notify the Agency, then the name, address, telephone number, fax number, e-mail address, and contact person of the third party have to provided.

(b) The identity of the substance with one or more information on name or other identifier of each substance, name(s) in the IUPAC nomenclature or other international chemical name(s), other names (usual name, trade name, abbreviation), EINECS or ELINCs number, CAS name and CAS number, other identity code, molecular and structural formula of each substance, information on optical activity and typical ratio of (stereo) isomers, molecular weight or molecular weight range, composition of each substance, degree of purity (%), nature of impurities (including isomers and by-products), and % of main impurities with the nature and order of magnitude (ppm, %) of any additives (e.g., stabilizing agents or inhibitors).
(c) The classification of substance(s) as per Parts 2–5 of Annex I [5].
(d) When a substance is classified in some but not in all hazard classes or differentiations, the reason being lack of data, inconclusive data, or insufficient data has to be indicated.
(e) Specific concentration limits or M-factors together with hazard assessment (as per Sections 1, 2, and 3 of Annex I [5] to Regulation (EC) No 1907/2006) [10].
(f) Label elements for the substance(s) with supplemental hazard statements. The information 1-6 shall not be notified if submitted as part of registration to Regulation (EC) No 1907/2006 [10], or if already notified by that notifier.

This information should be updated and notified to the Agency when there is a change to the classification and labelling of the substance in terms of change in the composition of the initial concentration of one or more of the hazardous constituents in concentrations at or above the limits or by the substitution or addition of one or more constituents in concentrations at or above the cutoff value (per Article 15) [16]. The substances placed on the market on or after 1 December 2010 should be notified to be included in the inventory within 1 month after placing on the market and substances placed on the market before this date should be notified to the Agency before that date. When the same substance gets different entries on the inventory, the notifiers and registrants must come to an agreement to make a single entry to the inventory and inform the Agency accordingly.

The classification and labelling inventory is a database established and maintained by the Agency. The information is submitted as part of the registration of the substance (Regulation (EC) No 1907/2006) [10] and is included in the inventory. The inventory information such as IUPAC nomenclature, name of the substance as given in EINECS, classification and labelling of the substance, physicochemical data of the substance together with pathways and environmental fate, results of the toxicological and ecotoxicological studies, derived no-effect level (DNEL) or predicted no-effect concentration (PNEC) of the substance, guidance of the safe use of the substance, and analytical methods to detect a dangerous substance upon exposure to humans and environment is made accessible to the public at free of cost over the Internet (Article 77(2)€ of Regulation (EC) No 1907/2006) [10]. The exception is provided where publication of information on the substance can potentially harm commercial interests of the notifier or registrant (Article 118 of Regulation (EC) 1906/2006) [10].

Apart from the information given above, additional information are made available free of access to the public over the Internet. These include the degree of purity of the substance and the identity of impurities and/or additives classified to be dangerous, the total tonnage band (i.e., 1–10 tons, 10–100 tons, 100–1000 tons, or over 1000 tons) within which a particular substance has been registered, study summaries on physicochemical data, toxicological data and ecotoxicological data, trade name(s) of the substance, IUPAC nomenclature of non-phase-in dangerous substances, and the IUPAC nomenclature of dangerous substances used as intermediate, in scientific research and development, and in product and process-related research. The Agency is obligated to update the information to the inventory as received. The Agency will have to include the following information on each entry wherever applicable: harmonized classification and labelling of the substance at Community level when entered in Part 3 of Annex VI [31], the joint entry between registrants for the same substance, agreed entry of two or more notifiers or registrants, entry differing from another entry on the inventory for the same substance.

6 Safety Data Sheet

The safety data sheet is a tool for communicating safety information on classified substances and preparations with relevant chemical safety reports from supply chain to the downstream user(s). Safety data sheet enables the users to take necessary measures for human health and safety measures at the workplace and protection of the environment. It also enables the employer to determine hazardous chemical agents at the workplace and to assess risk to health and safety of workers using them. The guidance for compiling safety data sheet is provided in Article 31 and Annex II of Regulation (EC) No. 1907/2006 [10].

The safety data sheet should be written in a clear and concise manner, and to achieve that, it has to be prepared by a competent person considering the needs of the users. Manufactures and importers who place the substances/mixtures on the market have the responsibility to place a person with appropriate training. The information can differ with wide range of properties of substances and mixtures. The information on some properties of no significance or technically impossible to provide should be stated so with reasons under each heading. The information on each hazardous property is to be given, and when particular hazard does not apply, then it should be given with negative results differentiating those with no information available. The date of issue of the safety data sheet should be given on the first page. When it is being revised, the changes shall be indicated as “Revision: (date).” Safety data sheets are required for substances or its preparations (e.g., metals in massive form, alloys, compressed gases, etc.) even when there are derogations in their labelling.

Safety data sheet should be given by the supplier of the substance to its recipient when the substance is classified as dangerous, persistent, bioaccumulative, toxic, and those subjected to authorization in accordance with Article 59 of Regulation

(EC) No. 1907/2006 [10]. The supplier should make sure that the chemical safety assessment information is consistent with what has been provided in the safety data sheet. The supplier should provide the recipient with safety data sheet on request when the preparation does not come under dangerous classification but contains ≥ 1% individual concentration by weight for non-gaseous preparations and ≥ 0.2% by volume for gaseous preparations where at least one substance is hazardous to human health or environmental, individual concentration ≥ 0.1% by weight for non-gaseous preparations with at least one substance that is persistent, bioaccumulative and toxic and when community workplace exposure limits are given for the substance.

The safety data sheet need not be provided for substances/preparations sold or given to the general public so long as sufficient measures with regard to health and environmental safety are provided, but this should be provided on request to downstream user or distributor. The safety data sheet should be printed in the official language of the Member of State in which the substance/preparation is on the market. All the relevant exposure scenarios obtained from doing the Chemical Safety report should be placed in the annex of the safety data sheet. The distributor and the downstream user can include and pass on possible exposure scenarios and use relevant information from the safety data sheet while compiling his/her own. The safety data sheet is provided free of charge in paper or electronically. The suppliers should update the safety data sheet without delay when new information affecting risk management measures and hazards are available, once authorization has been granted or refused, and once a restriction has been imposed. The new revised data sheet identified "Revision: (date)" should be provided free of cost on paper or electronically to formerly supplied end users within the preceding 12 months. Any update after registration should include the registration number.

Safety data sheet will include the following elements:

(a) *Identification of the substance/preparation and of the company/undertaking*: The identity of the substance should be the same as that provided in the label and consistent with the information given during registration (name and registration no.). All the uses of the substance or the preparation have to be indicated. When there are many uses, the most important or common uses need to be indicated with description of the use (e.g., flame retardant, antioxidant, etc.). In cases where chemical safety reports are required, then all the identified use is to be provided. The identity of the manufacturer, importer, or distributor who places the substance or the preparation on the market should be provided through address, phone number, and e-mail address. This person's identity should be in consistent with the details provided during registration. If the person is not located in the Member State where it is placed on market, then the person responsible in that Member State should provide their full address and telephone number. An emergency telephone number of the manufacturer, importer, or distributor and/or relevant advisory body (in case of health information) along with notification if this number is only available during office hours is warranted.

(b) *Hazard identification*: The substance or its preparation identified as hazardous to human and environment consistent with classification and labelling inventory should be clearly indicated. Distinction between dangerous and non-dangerous preparation should be clearly indicated (Directive 1999/45/EC). The most adverse physicochemical, health, and environmental effects and symptoms upon use and misuse of the substance/preparations should be described. Other hazards which may not be included for classification but contribute to the hazard like dustiness, cross-sensitization, suffocation, freezing, high potency for odor or taste, or environmental effects such as hazards to soil-dwelling organisms, ozone depletion, photochemical ozone creation potential, etc. should be given.

(c) *Composition/information on ingredients*: The information on composition and ingredients helps the end user to identify the hazard. It is not essential to provide the entire composition, but it is highly encouraged. Substances possessing hazard to human health and environment should be indicated with their concentration, concentration range in preparation, and community workplace exposure limits. The substances that are persistent and bioaccumulative are provided with concentration of an individual substance when equal to or greater than 0,1%. The preparations not classified as dangerous should be indicated when substances in the preparation are present in $\geq$ 1% by weight for non-gaseous preparations and $\geq$ 0,2% by volume for gaseous preparations of substances considered hazardous or $\geq$0,1% by weight of substances which are persistent, bioaccumulative, and toxic (PBT substance). A substance which does not meet the classification criteria of hazardous substance can still be included here if described as "PBT-substance" or "substance with community workplace exposure limits." The name, registration no., EINECS or ELINC no., CAS number, and IUPAC name shall be provided to be helpful. For substances with generic name, a precise chemical identifier is not necessary. When the person placing a preparation on the market should feel that the disclosure of the chemical identity of substance in safety data sheet can compromise the confidentiality of his/her intellectual property, then he/she may refer to that substance by the most important functional chemical groups or by an alternative name. Nevertheless, the chemical nature of the preparation should be communicated to ensure safe handling.

(d) *First aid measures*: Firstly, whether immediate medical attention is required has to be specified. The information given should be brief and easy to understand by victim, bystanders, and first-aiders. The symptoms and effects have to summarized. The instructions on what to be done on spot in case of accident and delayed effects to be expected upon exposure should be indicated. The information is divided as per the different routes of exposure (inhalation, skin and eye contact, ingestion). If professional assistance by a doctor is needed or advised, it should be communicated under this section. It is important to emphasize on provisions of immediate treatment at workplace to be available for some substances/preparations.

(e) *Firefighting measures*: The requirements for fighting a fire due to substance/preparation should be indicated with suitable extinguishing media, extinguishing media to be avoided, exposure hazards coming from substance/preparation through combustion and resulting gases, and special protective equipment for firefighters.

(f) *Accidental release measures*: Accidental release measures such as some personal precautions such as removal of ignition sources; provision of sufficient ventilation/respiratory protection; control of dust; prevention of skin and eye contact; environmental precautions such as keeping away from drains, surface, and groundwater and soil; possible need to alert neighborhood; methods for cleaning up such as use of absorbent material (sand, diatomaceous earth, acid binder, universal binder, sawdust); reduction of gases/fumes with water; and dilution are to be included in this section of safety data sheet along with indicators such as "never use, neutralize with, etc.".

(g) *Handling and storage*: The information in this section relates to the protection of health, safety, and environment together with assisting in devising suitable working procedures and organizational measures. Precautions and advice on safe handling like containment, local and general ventilation, measures to prevent aerosol and dust generation and fire, measures required to protect the environment (e.g., use of filters or scrubbers on exhaust ventilation, bunded area, measures for collection and disposal of spillages, etc.), and specific requirements like procedures or equipment which are prohibited or recommended relating to the substance or preparation with a brief description are given under this section. Storage conditions relating to type of material to be used in packaging of substance/preparation, design for storage rooms or vessels with retention walls and ventilation, quantity limits under storage, incompatible materials, storage temperature and humidity limit/range, light, inert gas, special electrical equipment, and prevention of static electricity should be advised. Products designed for specific use should have detailed and operational instructions and referenced by the industry.

(h) *Exposure controls/personal protection*: The occupational exposure limit values and/or biological limit values as given by the Member of the State where the substance/preparation are placed on the market are provided with information on recommended monitoring procedures. The derived no-effect level (DNEL) or predicted no-effect concentration for substances and all the constituents of substances used in the preparation should be given for exposure scenarios. Exposure controls, meaning the full range of specific risk management measures to be taken in order to minimize worker and environmental exposure, are provided under this section of the safety data sheet. Occupational exposure controls are used for carrying out risk to health and safety of workers for the substance/preparation. The hierarchy is such that first comes design of appropriate work processes and engineering controls with the use of adequate equipment and materials; second, the application of collective protection measures at source, such as adequate ventilation and appropriate organizational measures; and last, where exposure cannot be prevented, the use of individual

protection with personal protection equipment should be recommended. A risk assessment must be carried out to provide suitable information on control measures to be effective (Article 4 of Directive 98/24/EC). Specification on equipment to provide adequate protection in case of individual protection measures is required. Council Directive 89/686/EEC of 21 December 1989 accounts on laws relating to personal protective equipment: respiratory protection such as self-contained breathing apparatus, adequate masks, and filters to be used for dangerous gases, vapors, or dust; hand protection using gloves when handling substances/preparations together with type of material of the gloves and amount and duration of dermal exposure; safety glasses, goggles, and face shield in terms of eye protection; and aprons, boots, and full protective suit with specifying type and quality for skin protection. Environmental exposure control measures are a commitment to be fulfilled by the employer under Community environmental protection legislation.

(i) *Physical and chemical properties*: All information on substance/preparation regarding the appearance, odor, pH, boiling point/range, flash point, flammability, explosive properties, oxidizing properties, vapor pressure, relative density, solubility, water solubility, partition coefficient (n-octanol/water), viscosity, vapor density, and evaporation rate should be provided in order to install and enable proper control measures. Other safety parameters such as miscibility, fat solubility (solvent, oil to be specified), conductivity, melting point/melting range, gas, auto-ignition temperature, etc. also should be indicated in this section. These properties are to be determined using testing methods as given by Commission Regulation. When a particular hazard does not apply, then it should be indicated whether the results are negative or no information is available. For preparations, it is necessary to give properties of all the components in it.

(j) *Stability and reactivity*: The stability of the substance/preparation and hazardous reactions occurring under certain conditions and when released into the environment is provided in this section. Conditions and materials that might cause dangerous reaction such as temperature, pressure, light, shock, water, air, acids, bases, oxidizing agents, or any other specific substance are to be given, as well as hazardous products generated upon decomposition together with need for stabilizers, possibility of exothermic reaction, change in the physical appearance of the substance/preparation, products formed upon contact with water, and possibility of degradation of unstable products.

(k) *Toxicological information*: Complete and comprehensible description of various toxicological health effects when exposed to the substance/preparation is provided in this section. The information included will be dangerous-to-health effects upon exposure to the substance/preparation concluded from test data and experience. This should also be inclusive of delayed, immediate, and chronic effects from short- and long-term exposure such as sensitization, narcosis, carcinogenicity, mutagenicity, and reproductive toxicity (developmental toxicity and fertility). The routes of exposure inhalation, ingestion, and skin and eye contact and the symptoms related to physical, chemical, and

toxicological characteristics should be given in this section. Information on potential effects should be included such as toxicokinetics, metabolism and distribution, acute effects (acute toxicity, irritation, and corrosivity), sensitization, repeated dose toxicity, and CMR effects (carcinogenicity, mutagenicity, and toxicity for reproduction).

(l) *Ecological information*: The description of the possible effects and behavior and environmental fate of the substance/preparation in air, water, or soil along with the test data (e.g., LC50 fish $\leq$ 1 ml) is given under this section. This information should be the same when compared with those provided in the registration and Chemical Safety Report of the substance/preparation. Ecotoxicity includes data on aquatic toxicity, both acute and chronic for fish, crustaceans, algae, and other aquatic plants, and toxicity data on soil micro- and macro-organisms and other environmentally relevant organisms, such as birds, bees, and plants should be included. If the substance/preparation possesses inhibitory effects on the activity of micro-organisms, the possible impact on sewage treatment plant should be given. Mobility data when released into the environment includes known or predicted known or predicted distribution to environmental compartments, surface tension, and absorption/desorption. The persistence and degradability relate to the potential of the substance/preparation to degrade in environmental media by biodegradation, oxidation, hydrolysis, or other such processes. Degradation half-life is to be provided where available. The degradation of substance/preparation in sewage treatment plants is also to be provided. The potential of the substance/preparation to accumulate in biota and pass through the food chain is known as bioaccumulative potential. This is measured in terms of octanol-water partition coefficient (Kow) and bioconcentration factor (BCF) to be provided under this section of the safety data sheet. The persistent, bioaccumulative, and toxicity assessment data should also be included here. Any other adverse effects such as ozone depletion potential, photochemical ozone creation potential, endocrine-disrupting potential, and/or global warming potential might be mentioned. The ecotoxicological information should also be mentioned in accidental release measures, handling and storage, disposal considerations, transport information, and regulatory information of the safety data sheet.

(m) *Disposal considerations*: When the disposal of the substance/preparation possesses danger, then description of its residue and safe handling should be provided. The appropriate methods of disposal of the substance/preparation and contaminated packaging should be specified. This waste management specification should be consistent with exposure management in Chemical Safety Record.

(n) *Transport information*: The precautions to be taken by the user in terms of transport of the substance/preparation within or outside his/her premises are given under this heading. The transport regulations are provided by the International Maritime Dangerous Goods (IMDG) Code (sea route), Agreement concerning the International Carriage of Dangerous Goods by Road (ADR) code, RID code (by rail), and ICAO/IATA code (by air). The UN number, class,

proper shipping name, marine pollutant, and other applicable information should be provided during the transport of dangerous substance/preparation.

(o) *Regulatory information*: The chemical safety assessment for the substance/preparation should be indicated. The health, safety, and environmental information should be shown on the label. The specific provisions related to protection of man or the environment at the community level should be stated. The laws or measures which implement these provisions should also be mentioned.

(p) *Other information*: Any other information being of importance to the health and safety of the user and for the protection of the environment such as relevant R phrases, training advice, recommended restrictions on use, written references, technical contact point, and data source used for compiling safety data sheet should be provided. A revised safety data sheet should also indicate what has been added, deleted, or revised under this section unless indicated elsewhere.

Sample Safety Data Sheet

SECTION 1: IDENTIFICATION

Product identifier: Ethanol
Synonyms: Ethyl alcohol; ethyl hydrate
CAS No: 64-17-5
Details of the supplier of the safety data sheet:

Supplier:

Name
Address
Information contact
E-Mail (competent person)

Emergency telephone number:

SECTION 2: HAZARD(S) IDENTIFICATION

Classification:

Classification according to Regulation (EC) No 1272/2008 [CLP]	**Classification procedure**
Flam. Liq. 2, H225	On basis of test data
Eye Irrit. 2A, H319	Practical experience/human evidence

Label elements:
Labelling according to Regulation (EC) No 1272/2008 [CLP/GHS]

Hazard pictograms


GHS02


GHS07


GHS08

Signal word:
Danger

Hazard statements:

H225	Highly flammable liquid and vapor

Precautionary statements:

P210	Keep away from heat, hot surfaces, sparks, open flames and other ignition sources. No smoking.
P280	Wear protective gloves/protective clothing/eye protection/face protection.
P308+P311	IF exposed or concerned: Call a POISON CENTER/doctor.
P301+P330	IF SWALLOWED: Rinse mouth.
P303+P361+P353	IF ON SKIN (or hair): Take off immediately all contaminated clothing. Rinse skin with water/shower.
P304+P340	IF INHALED: Remove person to fresh air and keep comfortable for breathing.

Supplemental Hazard information:

SECTION 3. COMPOSITION/INFORMATION ON INGREDIENTS

Component	CAS No.	Weight %

Ethyl alcohol	64-17-5	60–70

SECTION 4: FIRST AID MEASURES

Description of first aid measures

General advice
Following inhalation
Following skin contact
Following eye contact
Following ingestion
Self-protection of the first aider

Most important symptoms and effects, both acute and delayed

Symptoms
Effects

Indication of any immediate medical attention and special treatment needed

Notes for the doctor
Special treatment

SECTION 5: FIREFIGHTING MEASURES

Extinguishing media

Suitable extinguishing media
Unsuitable extinguishing media

Special hazards arising from the substance or mixture

Hazardous combustion products

Advice for firefighters

Additional information

SECTION 6: ACCIDENTAL RELEASE MEASURES

Personal precautions, protective equipment, and emergency procedures

For non-emergency personnel

Protective equipment
Emergency procedures
For emergency responders
Personal protective equipment

Environmental precautions
Methods and material for containment and cleaning up
Reference to other sections

SECTION 7: HANDLING AND STORAGE

Precautions for safe handling

Conditions for safe storage, including any incompatibilities

Specific end uses

Recommendations
Specific end uses

SECTION 8: EXPOSURE CONTROLS/ PERSONAL PROTECTION

Control parameters

Exposure controls

SECTION 9. PHYSICAL AND CHEMICAL PROPERTIES

Information on basic physical and chemical properties

Appearance: Physical state: Color: Odor: Odor threshold:

	Value	Concentration	Method	Temperature	Pressure	Remark
pH						
Melting point/ freezing point						
Initial boiling point/ boiling range						

	Value	Concentration	Method	Temperature	Pressure	Remark
Flash point						
Evaporation rate						
Flammability (solid, gas)						
Vapor pressure						
Vapor density						
Relative density						
Solubility(ies)						

SECTION 10: STABILITY AND REACTIVITY

Reactive Hazard
Stability
Conditions to avoid

SECTION 11: TOXICOLOGICAL INFORMATION

Acute toxicity
Delayed and immediate effects as well as chronic effects from short- and long-term exposure

SECTION 12: ECOLOGICAL INFORMATION

Ecotoxicity
Persistence and degradability
Bioaccumulation/accumulation

SECTION 13: DISPOSAL CONSIDERATIONS

Waste disposal method

SECTION 14: TRANSPORT INFORMATION

UN No.
UN Proper shipping name
Transport hazard class(es)
Packing group

SECTION 15: REGULATORY INFORMATION

Safety, health and environmental regulations/legislation specific
EU regulations

Authorizations and/or restrictions on use
Authorizations
Restrictions on use
Restrictions of occupation

Other National regulations

SECTION 16: OTHER INFORMATION

Indication of changes
Abbreviations and acronyms
Key literature references and sources for data
Classification for mixtures and used evaluation method according to regulation (EC) 1207/2008 [CLP]
Relevant R-, H-, and EUH-phrases (number and full text)
Training advice
Further information

Bibliography

1. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, https://eurlex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:353:0001:1355:EN:PDF. Accessed 30 Jun. 2020
2. Chemsafetypro, https://www.chemsafetypro.com/Topics/EU/CLP_Regulation_EC_No_1272_2008.html. Accessed 30 Jun. 2020

3. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/1/adopted. Accessed 27 Jun. 2020
4. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/5/adopted. Accessed 30 Jun. 2020
5. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/6/adopted. Accessed 11 Jun. 2020
6. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/i/adopted. Accessed 7 Apr. 2020
7. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/8/adopted. Accessed 12 May 2020
8. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/7/adopted. Accessed 12 May 2020
9. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/9/adopted. Accessed 12 May 2020
10. legislation.gov.uk – Regulation (EC) No 1907/2006 of the European Parliament and of the Council. 18 Dec. 2006, https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2007:136:0003:0280:en:PDF. Accessed 12 May 2020
11. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/10/adopted. Accessed 9 Apr. 2020
12. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/11/adopted. Accessed 9 Apr. 2020
13. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/12/adopted. Accessed 27 May. 2020
14. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/13/adopted. Accessed 27 May. 2020
15. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/14/adopted. Accessed 14 Jun. 2020
16. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/15/adopted. Accessed 14 Jun. 2020
17. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/16/adopted. Accessed 16 Jun. 2020
18. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/vi/adopted. Accessed 7 Apr. 2020
19. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/17/adopted. Accessed 9 Apr. 2020

20. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/18/adopted. Accessed 9 Apr. 2020
21. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/19/adopted. Accessed 27 May. 2020
22. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/v/adopted. Accessed 7 Apr. 2020
23. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/20/adopted. Accessed 27 May. 2020
24. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/21/adopted. Accessed 14 Jun. 2020
25. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/iii/adopted. Accessed 23 Jun. 2020
26. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/iv/adopted. Accessed 23 Jun. 2020
27. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/22/adopted. Accessed 14 Jun. 2020
28. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/28/adopted. Accessed 16 Jun. 2020
29. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/25/adopted. Accessed 16 Jun. 2020
30. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/ii/adopted. Accessed 23 Jun. 2020
31. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/vi/adopted. Accessed 30 Jun. 2020
32. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/annex/v/adopted. Accessed 12 Jun. 2020
33. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/23/adopted. Accessed 16 Jun. 2020
34. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/29/adopted. Accessed 1 Jul. 2020
35. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/53/adopted. Accessed 29 Jun. 2020
36. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/31/adopted. Accessed 24 Jun. 2020

37. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/32/adopted. Accessed 24 Jun. 2020
38. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/33/adopted. Accessed 24 Jun. 2020
39. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/35/adopted. Accessed 29 Jun. 2020
40. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/39/adopted. Accessed 11 Jun. 2020
41. legislation.gov.uk – Regulation (EC) No 1272/2008 of the European Parliament and of the Council. 16 Dec. 2008, http://www.legislation.gov.uk/eur/2008/1272/article/40/adopted. Accessed 3 Jun. 2020

EU 2015/863: Restriction of Hazardous Substances (RoHS) -3

Harini Sriram and Indumathy Jagadeeswaran

1 Introduction

The European Parliament and the Council of the European Union, with regard to the Treaty on the Functioning of the European Union, a proposal from the European Commission, an opinion of the European Economic and Social Committee, an opinion of the Committee regions, and in accordance with the legislative procedure, has laid down restrictions on the use of hazardous substances in electrical and electronic equipment (EEE). This enables to prevent the occurrence of any barriers between the safety of human health and environment and trade and competition. The Council Resolution stresses that the Commission should pursue measures to combat cadmium pollution by restricting its use and encouraging alternatives. The Member States cannot effectively protect the environment and human health against pollutants because of the transboundary effects of pollutants. Hence, the European Parliament and Council recommend that measures should be taken at Union level such that the organic pollutants such as dioxins and furans should be identified and reduced and ultimately eliminated whenever possible [1]. The collection, treatment, recycling, and disposal of waste of EEE are essential to reduce problems arising from heavy metals and flame retardants. In spite of these regulations, waste from EEE (mercury, cadmium, lead, chromium VI, polybrominated biphenyls (PBB)) and polybrominated diphenyl ethers (PBDE) would be present in the disposal even if collected and recycled separately and pose a risk to human health and the environment [2]. The regulation takes into account the technical and economic feasibility of small and medium-sized enterprises (SMEs) to find an effective way of ensuring the

H. Sriram (✉)
National Dental Centre Singapore, Singapore, Singapore

I. Jagadeeswaran
Department of Biological Sciences, Southern Methodist University, Dallas, TX, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_15

reduction and substitution of hazardous substances in EEE. By restricting it can enhance profitability and the possibility of recycling waste EEE and reducing risk to health and environment at the recycling plants. In the measures provided under this regulation, international guidelines have to be considered and compactions and the assessment of scientific and technical information recommended. The measures have to be constantly reviewed and updated to achieve the chosen level of protection of human health and environment. Particularly, risks due to hexabromocyclododecane, bis(2-ethylhexyl) phthalate (DEHP), butyl benzyl phthalate (BBP), and dibutyl phthalate (DBP) should be prioritized. Therefore, Annexes XIV (List of substances subject to authorization) and XVII (Restrictions on the manufacture, placing on the market, and use of certain dangerous substances, preparations, and articles) to Regulation (EC) No 1907/2006 of the European Parliament and of the Council should be periodically reviewed and updated. This Directive also gives the general Union waste management legislation [3]. Definitions are also included to specify the scope and multipurpose character to determine the functions of EEE based on its characteristics, design, and marketing. Ecological designing specifications of EEE in energy-related products such as batteries and accumulators are also included in this directive, along with other Directives [4, 5]. Based on the scientific evidence it should be examined that substances classified as hazardous owing to their very small internal surface and structure such as nanomaterials and substituted with more environmentally friendly alternatives. This regulation holds the list of restricted substances in Annex II in coherence with Regulation (EC) No 1907/2006. This directive should not prevent the development of renewable energy technologies that cause no negative impact on health and the environment [6]. The substitutions of hazardous substances in EEE should consider the health and safety of users. Exemptions from these substitutions are made if it is not possible from a scientific and technical point of view, taking into account the availability of substitutes and the socioeconomic impact. The situation of SMEs should also be taken into account, and whether the negative environmental, health, and consumer safety impacts of the substitution outweigh the environmental, health, and consumer safety benefits of the substitution. This also applies to materials used in medical devices. The safety of the potential substitute for a medical or in vitro diagnostic device is not demonstrated, then it should be regarded to have a negative impact on socioeconomic, health, and consumer safety [7]. The exemptions for substitutions should be limited in order to facilitate the phasing-out of hazardous substances in EEE. The procedure for harmonizing conformity in the assessment of EEE is given under this directive and should conform with the Union legislation [8]. The EEE should be marked with CE markings when marketed and the market surveillance mechanisms govern the requirements for the accreditation and marketing of these products [9]. The Commission is empowered to implement power to ensure conformity with regard to guidelines laid out under this directive. The restrictions under this directive are governed both by the Member States and at Union Level.

2 Scope

This Directive applies to EEE listed under Annex I: Large household appliances, Small household appliances, IT, and telecommunications equipment, Consumer equipment, Lighting equipment, Electrical and electronic tools, Toys, leisure, and sports equipment, Medical devices, Monitoring and control instruments including industrial monitoring and control instruments, Automatic dispensers, and other EEE not covered by any of the categories above. The EEE outside the scope of Directive 2002/95/EC and that does not comply with this directive should not be available on the market after 22 July 2019. This directive will apply to the requirements of Union legislation on safety and health, and on chemicals, and Union waste management legislation. This directive does not apply to equipment used for security of the Member States such as arms, munitions, and war material intended for specifically military purposes, equipment sent into space, equipment that is specifically designed and installed to be a part of another type of equipment that is excluded or that does not fall within the scope of this Directive, large-scale stationary industrial tools, large-scale fixed installations, means of transport for persons or goods, excluding electric two-wheel vehicles, nonroad mobile machinery made available exclusively for professional use, active implantable medical devices, photovoltaic panels to produce energy from solar light for public, commercial, industrial, and residential applications, and equipment designed for research and development only available on a business-to-business basis.

3 Restriction Through Prevention

The Member States should make sure that EEE and their cables and spare parts do not contain substances such as lead (0.1%), mercury (0.1%), cadmium (0.01%), hexavalent chromium (0.1%), polybrominated biphenyls (PBB) (0.1%), polybrominated diphenyl ethers (PBDE) (0.1%), DEHP (0.1%), BBP (0.1%), DBP (0.1%), and diisobutyl phthalate (DIBP) (0.1%). The restriction of DEHP, BBP, DBP, and DIBP in EEE and their spare parts applies to medical devices, in vitro diagnostic medical devices, and medical and industrial monitoring and control instruments, from 22 July 2021. The restriction of DEHP, BBP, DBP, and DIBP does not apply to cables or spare parts of EEE used in the repair, reuse, and updating of functionalities or capacity before 22 July 2019. The restriction of DEHP, BBP, and DBP does not apply to toys, which are governed by Regulation (EC) No 1907/2006 [10, 11]. This list of substances applies to medical devices, monitoring and control instruments, in vitro diagnostic medical devices, and industrial monitoring and control instruments, placed on the market from 22 July 2014, 22 July 2016, and 22 July 2017 respectively. The restriction of this list of substances should not apply to cables and spare parts used in the repair, reuse, and updating of the functionalities and capacity of EEE (before 1 July 2006), medical devices (before 22 July 2014), in

vitro diagnostic medical devices, (before 22 July 2016), monitoring and control instruments (before 22 July 2014), industrial monitoring and control instruments (before 22 July 2017), and the EEE placed on the market that are already exempt. This list of substances does not apply to reused and recovered spare parts of EEE placed on the market before 1 July 2006 and fitted into equipment on the market from 1 July 2016, only if the reuse happens after audit in a closed-loop business-to-business return system and the customer is notified. The EEEs exempted from this substance restriction are given in Annex II and III of this derivative. To quote a few examples: mercury in single capped (compact) fluorescent lamps, lead in the glass of cathode ray tubes, cadmium and its compounds in one shot pellet type thermal cut-offs, etc.

4 Adaptation of the Annexes to Scientific and Technical Progress

To adapt Annexes III and IV, the Commission should adapt some measures to individual delegated acts. The inclusion of hazardous substances in EEEs that are exempt should ensure that it does not weaken the environmental and health protection. It should also be considered that the elimination or substitution of hazardous substances listed under Annex II via design changes should not make it scientifically or technically impractical, the substitution should be reliable, and the negative impact on the environment, health, and consumer safety should outweigh the benefits. The materials and components of EEE added to Annexes III and IV should take into account the availability of the substitutes and socio-economic impacts of the substitution. If these conditions are not fulfilled, these materials and components can be deleted from the list. The measures are adapted to include materials and components of EEE for large household appliances, small household appliances, IT and telecommunications equipment, consumer equipment, lighting equipment, electrical and electronic tools, toys, leisure and sports, and automatic dispenser equipment have validity of up to 5 years, and for medical devices, monitoring and control instruments, including industrial monitoring and control instruments, a validity of 7 years is granted. The exemptions laid out for applications in Annex III (e.g., mercury in single-capped (compact) fluorescent lamps, lead in the glass of cathode ray tubes, cadmium and its compounds in one shot pellet type thermal cut-offs, etc.) as at 21 July 2011, the maximum validity period (may be renewed) for large household appliances, small household appliances, IT and telecommunications equipment, consumer equipment, lighting equipment, electrical and electronic tools, toys, leisure and sports, and automatic dispenser equipment is 5 years from 21 July 2011 and for medical devices, monitoring and control instruments, including industrial monitoring and control instruments, is 7 years unless a shorter period is specified. The 7-year validity applies to applications included under Annex IV of this Directive (e.g., lead, cadmium, and mercury in detectors for ionizing radiation,

mercury in reference electrodes: low chloride mercury chloride, mercury sulfate and mercury oxide, lead, cadmium, and mercury in infra-red light detectors, etc.) unless a shorter period is specified. The Commission should provide a harmonized application format with guidelines for exemptions. The application should be submitted to the Commission for granting, renewing, or revoking an exemption by a manufacturer, the authorized representative of a manufacturer, or any economic operator in the supply chain with the name, address, and contact details of the applicant; information on the material or component and the specific uses of the substance in the material and component for which an exemption, or its revocation, is requested, and its particular characteristics; verifiable and referenced justification for an exemption, or its revocation; an analysis of possible alternative substances, materials, or designs on a life-cycle basis, including information about independent research, peer-review studies, and development activities by the applicant, and an analysis of the availability of such alternatives; information on the possible preparation for reuse or recycling of materials from waste EEE, and on the provisions relating to the appropriate treatment of waste [12]; the proposed actions to develop, request the development, and/or to apply possible alternatives including a timetable for such actions by the applicant; an indication of the information that should be regarded as proprietary accompanied by verifiable justification; a proposal with a precise and clear wording for the exemption and a summary of the application. The renewal application for an exemption should be made 18 months before the current exemption expires and the Commission should process the renewal within 6 months before the expiry unless other deadlines are specified. The Commission should notify the receipt of application within 15 days of the receiving date, inform the Member of States of the receipt of application with its details, write a summary of the application to notify the public, and evaluate the application. The Commission should make decisions after consulting economic operators, recyclers, treatment operators, environmental organizations, and employee and consumer associations and make the comments received publicly available. In the case of rejection/revocation of the renewal application, the existing exemption is deemed valid until 12–18 months after the decision date.

5 Review and Amendment of the List of Restricted Substances in Annex II

The Commission should periodically review and amend the list of restricted substances in Annex II in coherence with other legislations and made it publicly available [13]. These points should be considered after consultation with economic operators, recyclers, treatment operators, environmental organizations, and employee and consumer associations including: whether a substance is very small or has a very small internal or surface structure, causes a negative impact during EEE waste management operations, including the possibility of reuse and recycling,

uncontrolled or diffuse release of substances into the environment gives rise to hazardous residues, or transformation or degradation products through the preparation for reuse, recycling, or other treatment of materials from waste EEE, unacceptable exposure of workers involved in waste EEE collection or treatment processes, a substance is replacable by substitutes or alternative technology. The proposal to review and amend should at least the following information: precise and clear wording of the proposed restriction, references and scientific evidence for the restriction, information on the use of the substance or the group of similar substances in EEE, information on detrimental effects and exposure, in particular during waste EEE management operations, information on possible substitutes and other alternatives, their availability and reliability, justification for considering a Union-wide restriction, and socioeconomic assessment.

6 Obligations of Manufacturers

The manufacturers have an obligation to ensure that the EEE is designed and manufactured as per requirements set out by legislation. The technical documentation and internal production control should be created, updated, and maintained [14]. Manufacturers have to draw up an EU declaration of conformity and affix the CE marking on the finished product. The conformity assessment as per other Union legislations has to be demonstrated and documentation has to be drawn. The technical documentation and EU declaration conformity has to be kept for 10 years after the EEE has been placed on the market. The nonconforming products and recalled products have to be documented and the distributors informed. The type, batch, serial number, and other identification elements, along with the manufacturer's information, such as name, registered trade name or registered trade mark, and the contact address to be given on the EEE and in the case of a small EEE the details have to be on the accompanying package or document. Other Union legislation pertaining to the affixing of the manufacturer's name and address should be followed as well. When an EEE is found not to confirm to this Directive then the manufacturer should take the responsibility to make corrective measures, and to recall and inform the national authorities of the Member States in which it is marketed. The manufacturers have to provide all the information and documents to demonstrate the conformity of the EEE under this Directive to a competent national authority of the Member States in the language comprehensible to the authorities and cooperate with them.

7 Obligations of Authorized Representatives

The manufacturers can appoint authorized representatives with a written mandate. This should not include the technical documentation. The authorized representative is obligated to perform the tasks assigned as in the mandate. These shall include: maintaining the EU declaration of conformity and technical documentation at the disposal of the national authorities for 10 years, providing these documents to the national authorities on request, and cooperating with the authorities to ensure compliance with this Directive.

8 Obligations of Importers

Importers have an obligation to place on the market only those EEEs that comply with this Directive. The importers should also make sure that the conformity assessment, technical documents, and CE markings as per the regulations are done correctly by the manufacturer. If the importers feel that the EEE to be placed on the market is not up to the conformity standards they have to inform the manufacturer and the market surveillance authorities. The importers have to indicate their name, registered trade name and trademark, and contact address on the EEE and if the EEE is too small then it should be given in a separate accompanying document or package. The importers also have to keep a register of noncompliance EEEs and EEE recalls, and inform the distributors of the same. If the importers discover that the EEE does not conform to this Directive, they have an obligation to make sure that the corrective measures are taken or withdrawn or recalled, and also inform the national authorities of the Member States. The importer have to maintain the records of EU declaration conformity and technical documentation for 10 years and provide them with competent national authority upon request.

9 Obligations of Distributors

The distributors have to take appropriate care that the EEE made available on the market by them has proper CE markings and that the required document in the language is easily understood by the end-users in the Member State. The distributor is also obligated to confirm that the manufacturer and importer have complied with the requirements under this Directive. The nonconforming EEE should not be made available on the market by the distributor until it is corrected and the manufacturer, importer, and market surveillance authorities have been informed. The distributors, at the request of the national authority, should provide all information and documentation to demonstrate the conformity of the EEE.

Member States should ensure that an importer/distributor who places the EEE on the market is also considered a manufacturer under this Directive. The importers/distributors are subjected to the same obligations of the manufacturer when he/she places an EEE on the market under their name or trademark or modifies an EEE already on the market in that it requires compliance.

Member States should ensure that economic operators identify who has supplied them with an EEE and to whom they have supplied EEEs for 10 years after placing the EEE on the market to the market surveillance authorities.

10 EU Declaration of Conformity

The EU declaration of Conformity is the document that states whether the EEE meets the requirement set out under this derivative. The EU declaration of Conformity should have a model structure as given in this section and contain elements specified in Annex VI. It should be updated and translated into (a) language(s) required by the Member States. A single document should be drawn up in cases where other Union legislations require a conformity assessment procedure similar to this Directive that applies to the EEE. Once the EU declaration of conformity is drawn up it is the responsibility of the manufacturer to take responsibility for the compliance. It can be presumed by the Member States that the EEE marked with CE complies with this Directive. The materials, components, and EEE on which the compliance test and measurements have been performed should also conform with this Directive.

EU Declaration of Conformity

1. No … (unique identification of the EEE):
2. Name and address of the manufacturer or his authorized representative:
3. This declaration of conformity is issued under the sole responsibility of the manufacturer (or installer):
4. Object of the declaration (identification of the EEE allowing traceability. It may include a photograph, where appropriate):
5. The object of the declaration described above is in conformity with Directive 2011/65/EU of the European Parliament
   and of the Council of 8 June 2011 on the restriction of the use of certain hazardous substances in electrical and
   electronic equipment (*):
6. Where applicable, references to the relevant harmonized standards used or references to the technical specifications in
   relation to which conformity is declared:
7. Additional information:
   Signed for and on behalf of: .....
   ....
   (place and date of issue):
   (name, function) (signature)

11 Rules and Conditions for Affixing the CE Marking

The general principles for CE markings are given under a separate regulation [15]. The CE marking should be fixed visibly, legibly, and indelibly on the EEE or on the data plate unless it is not possible owing to the size and nature of the EEE. In that case it should be fixed to the packaging or accompanying document. It should be fixed before the EEE is available on the market. Member States should oversee the rules governing CE markings being correctly applied and actions taken when CE markings are done improperly. Member States apply penalties for infringements, including criminal sanctions. The penalties should be congruent with the gravity of the offence and discourages improper use.

12 Formal Objection to a Harmonized Standard

When a harmonized standard does not entirely satisfy the requirements it governs, the Member States or the Commission can escalate it to the Committee, giving reasons [16]. The Committee is formed by representatives of Member States and chaired by a representative of the Commission [17]. The opinion of the Committee is given on the notified issue after consulting with other European standardization bodies. After receiving the opinion, the Commission should publish, not publish, publish with restriction, maintain, maintain with restriction, or withdraw the standard. The Commission should notify the European standardization body and if required, request the revision of the harmonized standards. The market surveillance should be carried out by Member States following the appropriate regulations [18].

13 Exercise, Revocation, and Objection to Delegation

To achieve the objectives of this Directive, the Commission holds the power to adopt delegated acts [19]. The European Parliament should be notified of this empowerment and the Council and can extend it to a period of 5 years. The Commission should present a report 6 months before the end of the 50year period. This delegation is automatically renewed unless the European Parliament or Council revokes it. Whichever institution has decided to revoke the delegation of power with possible reasons should inform the other institution as well as the Commission before the final decision has been taken. Once decided, the delegation of power will cease immediately or at a later specified date and it should not interfere with the other delegated acts in force. This revocation should be published in the *Official Journal of the European Union*. The European Parliament or the Council can object to a delegated act within 2 months of the notification date and that period is extendable by another 2 months. Within the expiry of this period if neither the European

Parliament nor the Council objected to the delegated act it should be published and in force on the stated date. When there is an objection by either institution with proper reasons, the delegated act should not be published.

14 Penalties, Review, Repeal, and Entry into Force

The Member States should lay down effective and appropriate penalties to violation of provisions under this Directive and ensure their implementation. These penalties should be communicated along with any subsequent amendments to the Commission without any delay. By 22 July 2014, the Commission would have examined and amended this Directive and reported it to the European Parliament and the Council [20, 21]. Another general review has to be carried out by 22 July 2021 and submit a report or if applicable a legislative proposal. The Directive 2002/95/EC was amended and repealed from 3 January 2013. The repealed acts should be understood as a reference for this Directive as given under Annex VII. Any Directive has to be entered into force on the 20th day following its publication in the *Official Journal of the European Union*.

References

1. Regulation (EC) No 850/2004 of the European Parliament and of the Council of 29 April 2004 on persistent organic pollutants.
2. Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE).
3. Directive 2008/98/EC of the European Parliament and of the Council of 19 November 2008 on waste and repealing certain Directives and Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC.
4. Directive 2009/125/EC of the European Parliament and of the Council of 21 October 2009 establishing a framework for the setting of eco-design requirements for energy-related products.
5. Directive 2006/66/EC of the European Parliament and of the Council of 6 September 2006 on batteries and accumulators and waste batteries and accumulators and Regulation (EC) No 850/2004.
6. Directive 2009/28/EC of the European Parliament and of the Council of 23 April 2009 on the promotion of the use of energy from renewable sources.
7. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices (1) and Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.
8. Decision No 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products.

9. Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products.
10. Commission delegated directive (EU) 2015/863 of 31 March 2015 amending Annex II to Directive 2011/65/EU of the European Parliament and of the Council as regards the list of restricted substances.
11. Entry 51 of Annex XVII to Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
12. Annex II to Directive 2002/96/EC of the European Parliament and of the Council of 27 January 2003 on waste electrical and electronic equipment (WEEE)
13. Annexes XIV and XVII, Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC
14. Module A of Annex II to Decision No 768/2008/EC of the European Parliament and of the Council of 9 July 2008 on a common framework for the marketing of products, and repealing Council Decision 93/465/EEC.
15. Article 30 of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93.
16. Committee set up pursuant to Article 5 of Directive 98/34/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 June 1998 laying down a procedure for the provision of information in the field of technical standards and regulations.
17. REGULATION (EU) No 182/2011 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 February 2011 laying down the rules and general principles concerning mechanisms for control by Member States of the Commission's exercise of implementing powers.
18. Articles 15 to 29 of Regulation (EC) No 765/2008 of the European Parliament and of the Council of 9 July 2008 setting out the requirements for accreditation and market surveillance relating to the marketing of products and repealing Regulation (EEC) No 339/93.
19. Article 290 of the Treaty on the Functioning of the European Union in respect of amendments to Annex II, detailed rules for complying with maximum concentration values, and the adaptation of Annexes III and IV to technical and scientific progress.
20. COMMISSION DELEGATED DIRECTIVE (EU) 2015/863 of 31 March 2015 amending Annex II to Directive 2011/65/EU of the European Parliament and of the Council as regards the list of restricted substances.
21. COMMISSION DELEGATED DIRECTIVE (EU) 2016/585 of 12 February 2016 amending, for the purposes of adapting to technical progress, Annex IV to Directive 2011/65/EU of the European Parliament and of the Council as regards an exemption for lead, cadmium, hexavalent chromium, and polybrominated diphenyl ethers (PBDE) in spare parts recovered from and used for the repair or refurbishment of medical devices or electron microscopes.

EU 722/2012 – Animal Tissue Regulations in Effect for Some Medical Devices

Thamizharasan Sampath, Sandhiya Thamizharasan, Krithaksha V., and Prakash Srinivasan Timiri Shanmugam

Abbreviations

EC	European Commission
EEC	European Economic Community
EU	European Union
TSE	Transmissible spongiform encephalopathy
WHO	World Health Organization

Highlights

- The chapter provides information on EU regulation on medical device utilizing animal tissue.
- It also explains the risk of TSE infectious agents and its inactivation methods.

1 Introduction

Modern medical devices incorporate a range of materials into finished products, including animal tissues and other materials of animal origin. The type and quantities of materials of animal origin in medical devices vary. These materials can comprise a major part of the device (e.g., porcine/bovine heart valves, bone substitutes

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

Krithaksha V.
RMKSSS, RMK Group of Institutions, Chennai, Tamil Nadu, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_16

for use in orthopedic or dental applications and hemostatic devices), shall be used in the device manufacturing process (e.g., tallow derivatives such as stearates and oleates, fetal calf serum, culture media, enzymes), and can be a product coating/covering or impregnation (e.g., gelatine, collagen, heparin). Although animal materials can provide therapeutic and biocompatibility advantages over non-animal materials, their significant use in medical devices also introduces the risk of disease transmission from animals to humans. Most important concern is the potential transmission of transmissible spongiform encephalopathy (TSE), a devastating disease affecting the brains of susceptible species, including cattle, goats, and sheep, which can be transmitted to humans through contact with TSE-infected animal tissues and materials.

Article 1

(i) This Regulation lays down particular requirements in relation to the placing on the market and/or putting into service of medical devices, including active implantable medical devices, manufactured utilizing animal tissue which is rendered non-viable or non-viable products derived from animal tissue.
(ii) This Regulation shall apply to animal tissues, as well as their derivatives, originating from bovine, ovine, and caprine species, deer, elk, mink, and cats.
(iii) Collagen, gelatine, and tallow used for the manufacturing of medical devices shall meet at least the requirements as fit for human consumption laid down in Regulation (EC) No 1069/2009.
(iv) This Regulation shall not apply to any of the following:

- Tallow derivatives, processed under vigorous conditions
- Medical devices which are not intended to come into contact with the human body or which are intended to come into contact with intact skin only

Article 2

The following definitions apply in addition to the definitions set out in Directive 90/385/EEC and Directive 93/42/EEC:

Cell: The smallest organized unit of any living form which is capable of independent existence and of replacement of its own substance in a suitable environment
Tissue: An organization of cells, extracellular constituents, or both
Derivative: A material obtained from animal tissue through one or more treatments, transformations, or steps of processing
Non-viable: Having no potential for metabolism or multiplication
TSE: Transmissible spongiform encephalopathies
TSE infectious agents: Unclassified pathogenic agents which are capable of transmitting TSEs
Reduction, elimination, or removal: A process by which the number of TSE infectious agents is reduced, eliminated, or removed in order to prevent infection or pathogenic reaction
Inactivation: A process by which the ability to cause infection or pathogenic reaction by TSE infectious agents is reduced

Source country: The country or countries in which the animal was born, has been reared, and/or has been slaughtered

Starting materials: Raw materials or any other product of animal origin out of which, or with the help of which, the devices are produced

Article 3

- Before lodging an application for a conformity assessment pursuant to Article 9(1) of Directive 90/385/EEC or Article 11(1) of Directive 93/42/EEC, the manufacturer of medical devices referred to in Article 1(1) of this Regulation or his authorized representative shall carry out the risk analysis and risk management scheme set out in this Regulation.
- For custom-made devices and devices intended for clinical investigation which fall under Article 1(1), the statement of the manufacturer or his authorized representative and the documentation in accordance with Annex 6 to Directive 90/385/EEC or Annex VIII to Directive 93/42/EEC, respectively, shall also address compliance with the particular requirements set out in this Regulation.

Article 4

- Member States shall verify that bodies notified under Article 11 of Directive 90/385/EEC or Article 16 of Directive 93/42/EEC have up-to-date knowledge of the medical devices.
- Referred to in Article 1(1), in order to assess the conformity of those devices with the provisions of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and with the particular requirements laid down in this Regulation. Member States shall regularly verify that those bodies maintain the required up-to-date knowledge and expertise. Where, on the basis of that verification, it is necessary for a Member State to amend the tasks of a notified body, that Member State shall notify the Commission and the other Member States accordingly.
- The Member States shall inform the Commission and the other Member States regarding the outcome of the verification.

Article 5

- Conformity assessment procedures for medical devices referred to in Article 1(1) shall include the evaluation of compliance of the devices with the essential requirements of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and the particular requirements laid down to this Regulation.
- Notified bodies shall assess the documentation submitted by the manufacturer to verify that the benefits of the device outweigh the residual risks. Particular account shall be taken of:
  - The manufacturer's risk analysis and risk management process
  - The justification for the use of animal tissues or derivatives, taking into consideration lower-risk tissues or synthetic alternatives
  - The results of elimination and inactivation studies or results of the analysis of relevant literature
  - The manufacturer's control of the sources of raw materials, finished products, production process, testing, and subcontractors

– The need to audit matters related to the sourcing and processing of animal tissues and derivatives or processes to eliminate or inactivate pathogens, including those activities carried out by suppliers.

- Notified bodies shall, during the evaluation of the risk analysis and risk management in the framework of the conformity assessment procedure, take account of the TSE certificate of suitability issued by the European Directorate for the Quality of Medicines, hereinafter "TSE certificate of suitability," for starting materials, where available.

Where additional information is necessary to assess the suitability of the starting material for a given medical device, notified bodies may require submission of additional information to allow the evaluation.

- Before issuing an EC design-examination certificate or an EC type-examination certificate, the notified bodies shall, through their competent authority, hereinafter "coordinating competent authority," inform the competent authorities of the other Member States and the Commission of their assessment carried out summary evaluation report in accordance with this Regulation.
- The competent authorities of the Member States may submit comments on the summary evaluation report referred to in paragraph 4 within the following deadlines:

  (a) In relation to medical devices using starting materials for which a TSE certificate of suitability has been submitted, within 4 weeks from the date on which the notified body informed the coordinating competent authority
  (b) In relation to medical devices using starting materials for which a TSE certificate of suitability has not been submitted, within 12 weeks from the date on which the notified body informed the coordinating competent authority

The competent authorities of the Member States and the Commission may agree on shortening the time periods set out in points (a) and (b).

- They shall convey an explanation as regards this consideration, including any due justification not to take account of one or more of the comments received, and their final decisions to the coordinating competent authority, which shall then make these available to the Commission and the competent authorities from which comments were received.
- The manufacturer shall collect, evaluate, and submit to the notified body information regarding changes with regard to the animal tissue or derivatives used for the device or with regard to the TSE risk in relation to the device. Where such information leads to an increase of the overall TSE risk.

Article 6

- Member States shall take all necessary steps to ensure that medical devices referred to in Article 1(1) are placed on the market and/or put into service only if they comply with the provisions of Directive 90/385/EEC or Directive 93/42/EEC, respectively, and the particular requirements laid down in this Regulation.

Article 7

- Holders of EC design-examination certificates or EC-type examination certificates issued before 29 August 2013 for active implantable medical devices referred to in Article 1(1) shall apply to their notified body for a complementary EC design-examination certificate or EC-type examination certificate attesting compliance with the particular requirements laid down in this Regulation.
- Until 29 August 2014, Member States shall accept the placing on the market and the putting into service of active implantable medical devices referred to in Article 1(1) which are covered by an EC design-examination certificate or an EC-type examination certificate issued before 29 August 2013.

Article 8

- Directive 2003/32/EC is repealed with effect from 29 August 2013.
- References to the repealed Directive are to be construed as references to this Regulation. This Regulation enters into force on the 20th day following that of its publication in the Official Journal of the European Union. It shall apply from 29 August 2013 except for Article 4 which shall apply from the date of entry into force of this Regulation.

2 Risk Analysis and Risk Management

2.1 Justification for the Use of Animal Tissues or Derivatives

The manufacturer must justify, on the basis of his overall risk analysis and risk management strategy for a specific medical device, the decision to use animal tissues or derivatives, referred to in Article 1 (specifying animal species, tissues, and sourcing), taking into account the clinical benefit, potential residual risk, and suitable alternatives (such as lower-risk tissues or synthetic alternatives).

2.2 Process of Risk Assessment

In order to ensure a high level of protection for patients and users, the manufacturer of devices utilizing animal tissues or derivatives must implement an appropriate and well-documented risk analysis and risk management strategy, to address all relevant aspects relating to TSE. The manufacturer must identify the hazards and evaluate the risks associated with those tissues or derivatives, establish documentation on measures taken to minimize the risk of transmission, and demonstrate the acceptability of the residual risk associated with the device utilizing such tissues or derivatives, taking into account the intended use and the benefit of the device.

The safety of a device, in terms of its potential for passing on a TSE infectious agent, is dependent on all the factors described below to which the manufacturer

must analyze, evaluate, and manage. These measures in combination determine the device safety.

The manufacturer must consider the following key steps:

- Selecting starting materials (tissues or derivatives) considered appropriate regarding their potential contamination with TSE infectious agents taking into account further collection, handling, transport, storage, and processing.
- Applying a production process to remove or inactivate TSE infectious agents on controlled sourced tissues or derivatives.
- Maintaining a system to collect and evaluate production and post-production information regarding changes which may affect the assessment of the suitability.

In performing the risk analysis and risk management strategy, the manufacturer must give due consideration to the relevant published opinions adopted by the relevant European or international scientific committees or bodies, such as the Scientific Steering Committee (SSC), the European Food Safety Agency (EFSA), the European Medicines Agency (EMA), the World Organisation for Animal Health (OIE), and the World Health Organization (WHO).

2.3 Animals as a Source of Material

The TSE risk is related to the source species, strains, and nature of the starting tissue. As the accumulation of TSE infectivity occurs over an incubation period of several years, sourcing from young healthy animals is considered to be a factor reducing the risk. Risk animals such as fallen stock, emergency slaughtered, and TSE suspected animals must be excluded as a source of material.

Geographical Sourcing When assessing the risk of the source country, Commission Decision 2007/453/EC of 29 June 2007 establishing the BSE status of Member States or third countries or regions thereof according to their BSE risk is to be taken into account.

2.4 Nature of Starting Tissue

The manufacturer must take into account the classification of the risks relating to different types of starting tissue as defined in the WHO Guidelines on Tissue Infectivity Distribution in Transmissible Spongiform Encephalopathies (2006), as amended. Sourcing of animal tissue must be performed in such a manner as to maintain control over the traceability and integrity of source tissue. Where appropriate, the animals shall be subjected to veterinary ante- and postmortem inspection.

In addition, Regulation (EC) No 1069/2009 applies.

Without prejudice to the provision in the following paragraph, only category 3 material in accordance with Article 10 of Regulation (EC) No 1069/2009 shall be used.

The manufacturer must not source animal tissue or derivatives classified as potentially high TSE infective, unless sourcing of these materials is necessary in exceptional circumstances, taking into account the important benefit for the patient and the absence of an alternative starting tissue.

For bovine, ovine, and caprine animals, the list of specified risk material (SRM) laid down in Annex V to Regulation (EC) No 999/2001 is to be considered as being potentially of high TSE infectivity.

Slaughtering and processing controls to prevent cross-contamination: The manufacturer must ensure that the risk of cross-contamination during slaughtering, collection, processing, handling, storage, and transport is minimized.

2.5 Inactivation or Removal of TSE Infectious Agents

For devices which cannot withstand an inactivation or elimination process without undergoing unacceptable degradation, the manufacturer must rely principally on the control of sourcing. For other devices, if claims are made by the manufacturer for the ability of manufacturing processes to remove or inactivate TSE infectious agents, these must be substantiated by appropriate documentation. Relevant information from an analysis of appropriate scientific literature can be used to support inactivation and elimination factors, where the specific processes referred to in the literature are comparable to those used for the device. This search and analysis shall also cover the available scientific opinions that may have been adopted by a European or international scientific committee or body. These opinions are to serve as a reference, in cases where there are conflicting opinions.

If the literature search fails to substantiate the claims, the manufacturer must set up a specific inactivation or elimination study, as appropriate, on a scientific basis, and the following need to be considered:

- The identified hazard associated with the tissue
- Identification of the relevant model agents
- Rationale for the choice of the particular combinations of model agents
- Identification of step and/or stage chosen to eliminate or inactivate the TSE infectious agents
- Documentation of the parameters for any TSE inactivation or elimination validation study
- Calculation of the reduction factors

The manufacturer must apply appropriate documented procedures to ensure that the validated processing parameters are applied during routine manufacture. A final report must identify manufacturing parameters and limits that are critical to the effectiveness of the inactivation or elimination process.

Quantities of Animal Tissues or Derivatives Required to Produce One Unit of the Medical Device The manufacturer must evaluate the quantity of raw tissues or derivatives of animal origin required to produce a single unit of the medical device. The manufacturer must assess whether the production process has the potential to concentrate levels of TSE infectious agents present in the animal starting tissues or derivatives.

Tissues or Derivatives of Animal Origin Coming into Contact with the Patients and Users The manufacturer must consider:

- The maximum quantity of animal tissues or derivatives coming into contact with the patient or user when using a single medical device
- The contact area: its surface, type (e.g., skin, mucous tissue, brain), and condition (e.g., healthy or damaged)
- The type of the tissues or derivatives coming into contact with the patients or users
- -The period of time the device is intended to remain in contact with the body (including bioresorption effect)
- -The number of medical devices that could be used in a given procedure or, if possible, over the lifetime of a patient or user

Route of Administration In the risk assessment, the manufacturer must take into account the route of administration as indicated in the product information.

2.6 Review of the Risk Assessment

The manufacturer must establish and maintain a systematic procedure to review information gained about the medical device or similar devices in the post-production phase. The information must be evaluated for possible relevance to safety, especially in any of the following cases:

- Previously unrecognized hazards are identified.
- The estimated risk arising from a hazard has changed or is no longer acceptable.
- The original assessment is otherwise invalidated.

In the cases set out in the above points, the manufacturer shall feed back the results of the evaluation as an input to the risk management process. In the light of this new information, a review of the appropriate risk management measures for the device must be considered (including rationale for choosing an animal tissue or derivative). If there is a potential that the residual risk or its acceptability has changed, the impact on previously implemented risk control measures must be re-evaluated and justified. The results of this evaluation must be documented.

3 Evaluation by Notified Bodies

For the medical devices referred to in Article 1(1), manufacturers must provide to the notified bodies referred to in Article 4 all relevant information to allow evaluation of their risk analysis and risk management strategy in accordance with Article 5(2).

3.1 Information of the Notified Body Regarding Changes and New Information

Any change in relation to processes of sourcing, collection, handling, processing, and inactivation or elimination and any new information on TSE risk collected by the manufacturer and relevant for the medical device that could modify the result of the manufacturer's risk assessment must be transmitted to the notified body and, where applicable, need to be approved by the notified body prior to its implementation.

3.2 Renewal of Certificates

In the context of its decision regarding the extension for a further period of maximum 5 years of an EC design-examination certificate or an EC-type examination certificate in accordance with Article 9(8) of Directive 90/385/EEC or Article 11(11) of Directive 93/42/EEC, respectively, the notified body shall review for the purpose of this Regulation at least in the following aspects:

- Updated justification for the use of animal tissue or derivative, including a comparison with lower-risk tissues or synthetic alternatives
- Updated risk analysis
- Updated clinical evaluation
- Updated test data and/or rationales, for example, in relation to the current harmonized standards
- Identification of any changes made since the issue of the original certificate (or last renewal) that could impact the TSE risk
- Evidence that the design dossier remains state of the art in relation to TSE risks

Increase of the Overall TSE Risk Where on the basis of information submitted in accordance with Sects. 3.1 or 3.2 a notified body establishes that the overall TSE risk in relation to a medical device is increased, this notified body shall follow the procedure set out in Article 5.

3.3 Rigorous Processes for Tallow Derivatives

- Trans-esterification or hydrolysis at not less than 200 °C for not less than 20 min under pressure (glycerol, fatty acids, and fatty acid esters production)
- Saponification with NaOH 12 M (glycerol and soap production)
- Batch process: at not less than 95 °C for not less than 3 h
- Continuous process: at not less than 140 °C, under pressure for not less than 8 min or equivalent
- Distillation at 200 °C

3.4 Summary Evaluation Report in Accordance with Article 5(4) of Regulation (EU) No 722/2012

Details relating to the submitting notified body:

1. Name of the notified body
2. Notified body number
3. Country
4. Sent by
5. Contact person
6. Telephone
7. Fax
8. E-mail
9. Client reference(name of the manufacturer and, if applicable, of authorized representative)
10. Confirmation that, in accordance with Article 11 of Directive 90/385/EEC AND Article 16 of Directive 93/42/EEC, respectively, and Article 4 of Regulation(EU) No 722/2012, the submitting notified body has been designated by its competent authority for the conformity assessment of:

    ○ Active implantable medical devices manufactured utilizing tissues of animal origin subject to Regulation (EU) No 722/2012
    ○ Medical devices manufactured utilizing tissues of animal origin subject to Regulation (EU) No 722/2012

Data relating to the (active implantable) medical devices:

11. (a) ○ Active implantable medical devices ○ other medical devices

    (b) Product description and composition

12. Information on intended use
13. Starting material

(a) EDQM certificate available ○ Yes ○ No
(if the EDQM certificate is available, it must be submitted with this summary evaluation report)
(b) Information regarding

– The nature of the starting tissue(s)
– Animal species(s)
– Geographical source(s)

14. A description of key the elements adopted to minimize the risk of infection
15. An estimate of the TSE risk arising from the use of the product, taking into account the likelihood of contamination of the product and the nature and duration of patient exposure
16. A justification for the use of animal tissues or derivatives in the medical device, including a rationale for the acceptability of the overall TSE risk estimate, the evaluation of alternative materials, and the expected clinical benefit
17. The approach to the auditing of source establishments and suppliers for the animal material used by the device manufacturer

Notified body statement

18. Conclusion of this assessment:
Based on the evaluation of data and the assessment process, it is our preliminary decisions that the application meets the requirements of conformity with:
○ Council Directive 90/385/EEC and Regulation (EU) No 722/2012
○ Council Directive 93/42/EEC

Date of Submission

19. This report was sent on…….to the Coordinating Competent Authority of…….to inform the Competent Authorities of the other Member States and the Commission and to seek their comments, if any.

Reference

1. EU – 722/2012, Commission Regulation Concerning particular requirements as regards the requirements laid down in Council Directives 90/385/EEC and 93/42/EEC with respect to active implantable medical devices and medical devices manufactured utilising tissues of animal origin, 09.08.2012, Official journal of European Union, 212:3–12.

EU 2017/746 – In Vitro Diagnostic Medical Devices

Thamizharasan Sampath, Sandhiya Thamizharasan, and Prakash Srinivasan Timiri Shanmugam

Abbreviations

CE	European conformity
CS	Common specifications
EMA	European Medicines Agency
EU	European Union
EUDAMED	European Database on Medical Devices
IVDR	In Vitro Diagnostic Medical Devices Regulations
MDCG	Medical Device Coordination Group
NANDO	New Approach Notified and Designated Organisations
PMPF	Post-market Performance Follow up
PSUR	Periodic Safety Update Report
SRN	Single Registration Number
UDI	Unique Device Identification
UDI-DI	UDI Device Identifier
UDI-PI	UDI Production Identifier

Highlights

- The chapter provides information about EU regulatory process involved in in vitro diagnostic medical device manufacturing process.
- It also explains the articles laid for nomenclature, identification, design, and development of in vitro diagnostic medical devices.

T. Sampath (✉)
Department of Pharmacology, Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

S. Thamizharasan
Maitri College of Dentistry & Research Centre, Anjora, Durg, Chhattisgarh, India

P. S. Timiri Shanmugam
Global Product Safety & Toxicology, Avanos Medical, Inc., Alpharetta, GA, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_17

1 Scope

1. This Regulation lays down rules concerning the placing on the market, making available on the market, or putting into service of in vitro diagnostic medical devices for human use and accessories for such devices in the Union.
2. For the purposes of this Regulation, in vitro diagnostic medical devices and accessories for in vitro diagnostic medical devices shall hereinafter be referred to as "devices."
3. This Regulation does not apply to:
   (a) Products for general laboratory use or research-use only products, unless such products, in view of their characteristics, are specifically intended by their manufacturer to be used for in vitro diagnostic examination
   (b) Invasive sampling products or products which are directly applied to the human body for the purpose of obtaining a specimen
   (c) Internationally certified reference materials
   (d) Materials used for external quality assessment schemes
4. This Regulation shall not affect the right of a Member State to restrict the use of any specific type of device in relation to aspects not covered by this Regulation.
5. This Regulation shall not affect national law concerning the organization, delivery, or financing of health services and medical care, such as the requirement that certain devices may only be supplied on a medical prescription, the requirement that only certain health professionals or healthcare institutions may dispense or use certain devices, or that their use be accompanied by specific professional counselling.
6. Nothing in this Regulation shall restrict the freedom of the press or the freedom of expression in the media insofar as those freedoms are guaranteed in the Union and in the Member States, in particular under Article 11 of the Charter of Fundamental Rights of the European Union.

2 Definitions

In vitro diagnostic medical device: any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, or software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:

- Concerning a physiological or pathological process or state
- Concerning congenital physical or mental impairments
- Concerning the predisposition to a medical condition or a disease

- To determine the safety and compatibility with potential recipients
- To predict treatment response or reactions
- To define or monitoring therapeutic measures

Specimen receptacle: a device, whether of vacuum type or not, specifically intended by its manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination

Accessory for an in vitro diagnostic medical device: an article which, while not being itself an in vitro diagnostic medical device, is intended by its manufacturer to be used together with one or several particular in vitro diagnostic medical device(s) to specifically enable the in vitro diagnostic medical device(s) to be used in accordance with its/their intended purpose(s) or to specifically and directly assist the medical functionality of the in vitro diagnostic medical device(s) in terms of its/their intended purpose(s)

Device for self-testing: any device intended by the manufacturer to be used by laypersons, including devices used for testing services offered to laypersons by means of information society services

Device for near-patient testing: any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional

Generic device group: a set of devices having the same or similar intended purposes or a commonality of technology allowing them to be classified in a generic manner not reflecting specific characteristics

Single-use device: a device that is intended to be used during a single procedure

Falsified device: any device with a false presentation of its identity and/or of its source and/or its CE marking certificates or documents relating to CE marking procedures. This definition does not include unintentional non-compliance and is without prejudice to infringements of intellectual property rights

Kit: a set of components that are packaged together and intended to be used to perform a specific in vitro diagnostic examination, or a part thereof

Intended purpose: the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use, or in promotional or sales materials or statements or as specified by the manufacturer in the performance evaluation

Label: the written, printed, or graphic information appearing either on the device itself or on the packaging of each unit or on the packaging of multiple devices

Instructions for use: the information provided by the manufacturer to inform the user of a device's intended purpose and proper use and of any precautions to be taken

Unique Device Identifier (UDI): a series of numeric or alphanumeric characters that is created through internationally accepted device identification and coding standards and that allows unambiguous identification of specific devices on the market

Risk: the combination of the probability of occurrence of harm and the severity of that harm

Benefit-risk determination: the analysis of all assessments of benefit and risk of possible relevance for the use of the device for the intended purpose, when used in accordance with the intended purpose given by the manufacturer

Putting into service: the stage at which a device, other than a device for performance study, has been made available to the final user as being ready for use on the Union market for the first time for its intended purpose

Manufacturer: a natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured, or fully refurbished and markets that device under its name or trademark

Authorized representative: any natural or legal person established within the Union who has received and accepted a written mandate from a manufacturer, located outside the Union, to act on the manufacturer's behalf in relation to specified tasks with regard to the latter's obligations under this Regulation

Importer: any natural or legal person established within the Union that places a device from a third country on the Union market

Distributor: any natural or legal person in the supply chain, other than the manufacturer or the importer, that makes a device available on the market, up until the point of putting into service

User: any healthcare professional or layperson who uses a device

Layperson: an individual who does not have formal education in a relevant field of healthcare or medical discipline

Conformity assessment: the process demonstrating whether the requirements of this Regulation relating to a device have been fulfilled

Conformity assessment body: a body that performs third-party conformity assessment activities including calibration, testing, certification, and inspection

Notified body: a conformity assessment body designated in accordance with this Regulation

CE marking of conformity: a marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in this Regulation and other applicable Union harmonization legislation providing for its affixing

Clinical evidence: clinical data and performance evaluation results, pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer

Clinical benefit: the positive impact of a device related to its function, such as that of screening, monitoring, diagnosis, or aid to diagnosis of patients, or a positive impact on patient management or public health

Performance evaluation: an assessment and analysis of data to establish or verify the scientific validity, the analytical, and, where applicable, the clinical performance of a device

Device for performance study: a device intended by the manufacturer to be used in a performance study. A device intended to be used for research purposes, without any medical objective, shall not be deemed a device for performance study

Interventional clinical performance study: a clinical performance study where the test results may influence patient management decisions and/or may be used to guide treatment

Subject: an individual who participates in a performance study and whose specimen(s) undergo in vitro examination by a device for performance study and/or by a device used for control purposes

Investigator: an individual responsible for the conduct of a performance study at a performance study site

Diagnostic specificity: the ability of a device to recognize the absence of a target marker associated with a particular disease or condition

Diagnostic sensitivity: the ability of a device to identify the presence of a target marker associated with a particular disease or condition

Likelihood ratio: the likelihood of a given result arising in an individual with the target clinical condition or physiological state compared to the likelihood of the same result arising in an individual without that clinical condition or physiological state

Calibrator: a measurement reference material used in the calibration of a device

Control material: a substance, material, or article intended by its manufacturer to be used to verify the performance characteristics of a device

Sponsor: any individual, company, institution, or organization which takes responsibility for the initiation, management, and setting up of the financing of the performance study

Device deficiency: any inadequacy in the identity, quality, durability, reliability, safety, or performance of a device for performance study, including malfunction, use errors, or inadequacy in information supplied by the manufacturer

Recall: any measure aimed at achieving the return of a device that has already been made available to the end user

Withdrawal: any measure aimed at preventing a device in the supply chain from being further made available on the market

Corrective action: action taken to eliminate the cause of a potential or actual nonconformity or other undesirable situation

Field safety corrective action: corrective action taken by a manufacturer for technical or medical reasons to prevent or reduce the risk of a serious incident in relation to a device made available on the market

Field safety notice: a communication sent by a manufacturer to users or customers in relation to a field safety corrective action

3 Regulatory Status of Products and Counselling

Regulatory Status of Products (Article 3)

1. A duly substantiated request of a Member State, the Commission shall, after consulting the Medical Device Coordination Group established under Article 103 of Regulation (EU) 2017/745 (MDCG), by means of implementing acts,

determine whether or not a specific product, or category or group of products, falls within the definitions of "in vitro diagnostic medical device" or "accessory for an in vitro diagnostic medical device."
2. The Commission shall ensure that Member States share expertise in the fields of in vitro diagnostic medical devices, medical devices, medicinal products, human tissues and cells, cosmetics, biocides, food, and, if necessary, other products, in order to determine the appropriate regulatory status of a product, or category or group of products.
3. When deliberating on the possible regulatory status as a device of products involving medicinal products, human tissues and cells, biocides, or food products, the Commission shall ensure an appropriate level of consultation of the European Medicines Agency (EMA), the European Chemicals Agency, and the European Food Safety Authority, as relevant.

Genetic Information, Counselling, and Informed Consent (Article 4)

1. Member States shall ensure that where a genetic test is used on individuals, in the context of healthcare and for the medical purposes of diagnostics, improvement of treatment, predictive, or prenatal testing, the individual being tested or, where applicable, his or her legally designated representative is provided with relevant information on the nature, the significance, and the implications of the genetic test, as appropriate.
2. Member States shall, in particular, ensure that there is appropriate access to counselling in the case of the use of genetic tests that provide information on the genetic predisposition for medical conditions and/or diseases which are generally considered to be untreatable according to the state of science and technology.
3. Nothing in this Article shall prevent Member States from adopting or maintaining measures at the national level which are more protective of patients, more specific or which deal with informed consent.

4 Marketing and Service

Placing on the Market and Putting into Service (Article 5)

- A device may be placed on the market or put into service only if it complies with this Regulation when duly supplied and properly installed, maintained, and used in accordance with its intended purpose.
- Devices that are manufactured and used within health institutions, with the exception of devices for performance studies, shall be considered as having been put into service.
- The requirements of this Regulation shall not apply to devices manufactured and used only within health institutions established in the Union, provided that all of the following conditions are met:

  (a) The devices are not transferred to another legal entity.

(b) Manufacture and use of the devices occur under appropriate quality management systems.
(c) The laboratory of the health institution is compliant with standard EN ISO 15189 or where applicable national provisions, including national provisions regarding accreditation.
(d) The health institution justifies in its documentation that the target patient group's specific needs cannot be met, or cannot be met at the appropriate level of performance by an equivalent device available on the market.

Distance Sales (Article 6)
Without prejudice to national law regarding the exercise of the medical profession, a device that is not placed on the market but used in the context of a commercial activity, whether in return for payment or free of charge, for the provision of a diagnostic or therapeutic service offered by means of information society services or by other means of communication, directly or through intermediaries, to a natural or legal person established in the Union shall comply with this Regulation.

Claims (Article 7)
In the labelling, instructions for use, making available, putting into service, and advertising of devices, it shall be prohibited to use text, names, trademarks, pictures, and figurative or other signs that may mislead the user or the patient with regard to the device's intended purpose, safety, and performance by:

(a) Ascribing functions and properties to the device which the device does not have
(b) Creating a false impression regarding treatment or diagnosis, functions, or properties which the device does not have
(c) Failing to inform the user or the patient of a likely risk associated with the use of the device in line with its intended purpose
(d) Suggesting uses for the device other than those stated to form part of the intended purpose for which the conformity assessment was carried out

Use of Harmonized Standards (Article 8)
Devices that are in conformity with the relevant harmonized standards, or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards. References in this Regulation to harmonized standards shall also include the monographs of the European Pharmacopoeia adopted in accordance with the Convention on the Elaboration of a European Pharmacopoeia, provided that references to those monographs have been published in the Official Journal of the European Union.

Common Specifications (Article 9)
Where no harmonized standards exist or where relevant harmonized standards are not sufficient, or where there is a need to address public health concerns, the Commission, after having consulted the MDCG, may, by means of implementing acts, adopt common specifications (CS) in respect of the general safety and

performance requirements. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107.

General Obligations of Manufacturers (Article 10)
When placing their devices on the market or putting them into service, manufacturers shall ensure that they have been designed and manufactured in accordance with the requirements of this Regulation. Manufacturers shall establish, document, implement, maintain a system for risk management, and conduct a performance evaluation in accordance with the requirements set out in Article 56. Manufacturers shall draw up and keep up to date the technical documentation for those devices. The technical documentation shall be such as to allow the conformity of the device with the requirements of this Regulation to be assessed. Manufacturers shall ensure that procedures are in place to keep series production in conformity with the requirements of this Regulation. Changes in product design or characteristics and changes in the harmonized standards or CS by reference to which the conformity of a product is declared shall be adequately taken into account in a timely manner. Manufacturers of devices, other than devices for performance study, shall establish, document, implement, maintain, keep up to date, and continually improve a quality management system that shall ensure compliance with this Regulation in the most effective manner and in a manner that is proportionate to the risk class and the type of device.

Authorized Representative (Article 11)
Where the manufacturer of a device is not established in a Member State, the device may only be placed on the Union market if the manufacturer designates a sole authorized representative. The designation shall constitute the authorized representative's mandate, and it shall be valid only when accepted in writing by the authorized representative and shall be effective at least for all devices of the same generic device group. The authorized representative shall perform the tasks specified in the mandate agreed between it and the manufacturer. The authorized representative shall provide a copy of the mandate to the competent authority, upon request.

Change of Authorized Representative (Article 12)
The detailed arrangements for a change of authorized representative shall be clearly defined in an agreement between the manufacturer, where practicable the outgoing authorized representative, and the incoming authorized representative. That agreement shall address at least the following aspects: (a) the date of termination of the mandate of the outgoing authorized representative and date of beginning of the mandate of the incoming authorized representative; (b) the date until which the outgoing authorized representative may be indicated in the information supplied by the manufacturer, including any promotional material; (c) the transfer of documents, including confidentiality aspects and property rights; and (d) the obligation of the outgoing authorized representative after the end of the mandate to forward to the manufacturer or incoming authorized representative any complaints or reports from healthcare professionals, patients, or users about suspected incidents related to a device for which it had been designated as authorized representative.

General Obligations of Importers (Article 13)
Importers shall place on the Union market only devices that are in conformity with this Regulation. In order to place a device on the market, importers shall verify that (a) the device has been CE marked and that the EU declaration of conformity of the device has been drawn up; (b) a manufacturer is identified and that an authorized representative in accordance with Article 11 has been designated by the manufacturer; (c) the device is labelled in accordance with this Regulation and accompanied by the required instructions for use; and (d), where applicable, a UDI has been assigned by the manufacturer in accordance with Article 24.

General Obligations of Distributors (Article 14)
When making a device available on the market, distributors shall, in the context of their activities, act with due care in relation to the requirements applicable. Before making a device available on the market, distributors shall verify that all of the following requirements are met:

(a) The device has been CE marked, and the EU declaration of conformity of the device has been drawn up.
(b) The device is accompanied by the information to be supplied by the manufacturer in accordance with Article 10.
(c) For imported devices, the importer has complied with the requirements set out in Article 13.

Person Responsible for Regulatory Compliance (Article 15)
Manufacturers shall have available within their organization at least one person responsible for regulatory compliance who possesses the requisite expertise in the field of in vitro diagnostic medical devices. The requisite expertise shall be demonstrated by either of the following qualifications: (a) a diploma, certificate, or other evidence of formal qualification, awarded on completion of a university degree or of a course of study recognized as equivalent by the Member State concerned, in law, medicine, pharmacy, engineering, or another relevant scientific discipline, and at least 1 year of professional experience in regulatory affairs or in quality management systems relating to in vitro diagnostic medical devices; and (b) 4 years of professional experience in regulatory affairs or in quality management systems relating to in vitro diagnostic medical devices.

Cases in Which Obligations of Manufacturers Apply to Distributors (Article 16)
A distributor, importer, or other natural or legal person shall assume the obligations incumbent on manufacturers if it does any of the following: (a) makes available on the market a device under its own name, registered trade name, or registered trade mark, except in cases where a distributor or importer enters into an agreement with a manufacturer whereby the manufacturer is identified as such on the label and is responsible for meeting the requirements placed on manufacturers in this Regulation; (b) changes the intended purpose of a device already placed on the market or put into service; and (c) modifies a device already placed on the market or put into

service in such a way that compliance with the applicable requirements may be affected.

EU Declaration of Conformity (Article 17)
The EU declaration of conformity shall state that the requirements specified in this Regulation have been fulfilled. The manufacturer shall continuously update the EU declaration of conformity. Where concerning aspects not covered by this Regulation, devices are subject to other Union legislation which also requires an EU declaration of conformity by the manufacturer that fulfilment of the requirements of that legislation has been demonstrated, a single EU declaration of conformity shall be drawn up in respect of all Union acts applicable to the device. The declaration shall contain all the information required for identification of the Union legislation to which the declaration relates. By drawing up the EU declaration of conformity, the manufacturer shall assume responsibility for compliance with the requirements of this Regulation and all other Union legislation applicable to the device.

CE Marking of Conformity (Article 18)
Devices, other than devices for performance studies, considered to be in conformity with the requirements of this Regulation shall bear the CE marking of conformity. The CE marking shall be affixed visibly, legibly, and indelibly to the device or its sterile packaging. Where such affixing is not possible or not warranted on account of the nature of the device, the CE marking shall be affixed to the packaging. The CE marking shall also appear in any instructions for use and on any sales packaging.

Devices for Special Purposes (Article 19)
Member States shall not create obstacles to devices for performance study being supplied for that purpose to laboratories or other institutions, if they meet the conditions laid down in Articles 57 to 76, and in the implementing acts adopted pursuant to Article 77. At trade fairs, exhibitions, demonstrations, or similar events, Member States shall not create obstacles to the showing of devices which do not comply with this Regulation, provided that a visible sign clearly indicates that such devices are intended for presentation or demonstration purposes only and cannot be made available until they have been brought into compliance with this Regulation.

Parts and Components (Article 20)
Any natural or legal person who makes available on the market an item specifically intended to replace an identical or similar integral part or component of a device that is defective or worn in order to maintain or restore the function of the device without changing its performance or safety characteristics or its intended purpose shall ensure that the item does not adversely affect the safety and performance of the device. Supporting evidence shall be kept available for the competent authorities of the Member States. An item that is intended specifically to replace a part or component of a device and that significantly changes the performance or safety characteristics or the intended purpose of the device shall be considered a device and shall meet the requirements laid down in this Regulation.

Free Movement (Article 21)
Member States shall not refuse, prohibit, or restrict the making available on the market or putting into service within their territory of devices which comply with the requirements of this Regulation.

5 Identification, Traceability, and Registration of Devices

Identification Within the Supply Chain (Article 22)
Distributors and importers shall co-operate with manufacturers or authorized representatives to achieve an appropriate level of traceability of devices. Economic operators shall be able to identify the following to the competent authority, for the period referred to in Article 10: (a) any economic operator to whom they have directly supplied a device; (b) any economic operator who has directly supplied them with a device; and (c) any health institution or healthcare professional to which they have directly supplied a device.

Medical Devices Nomenclature (Article 23)
To facilitate the functioning of the European database on medical devices as referred to in Article 33 of Regulation (EU) 2017/745, the Commission shall ensure that an internationally recognized medical devices nomenclature is available free of charge to manufacturers and other natural or legal persons required by this Regulation to use that nomenclature. The Commission shall also endeavor to ensure that that nomenclature is available to other stakeholders free of charge, where reasonably practicable.

Unique Device Identification System (Article 24)
The UDI is a series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard. It allows the unambiguous identification of a specific device on the market. The UDI is comprised of (i) a UDI device identifier ("UDI-DI") specific to a manufacturer and a device providing access to the information and (ii) a UDI production identifier ("UDI-PI") that identifies the unit of device production and if applicable the packaged devices. The Commission shall, by means of implementing acts, designate one or several entities to operate a system for assignment of UDIs pursuant to this Regulation ("issuing entity"). That entity or those entities shall satisfy all of the following criteria: (a) the entity is an organization with legal personality; (b) its system for the assignment of UDIs is adequate to identify a device throughout its distribution and use in accordance with the requirements of this Regulation; (c) its system for the assignment of UDIs conforms to the relevant international standards; and (d) the entity gives access to its system for the assignment of UDIs to all interested users in accordance with a set of predetermined and transparent terms and conditions.

UDI Database (Article 25)
The Commission, after consulting the MDCG, shall set up and manage a UDI database in accordance with the conditions and detailed arrangements provided for in Article 28 of Regulation (EU) 2017/745.

Registration of Devices (Article 26)
Before placing a device on the market, the manufacturer shall, in accordance with the rules of the issuing entity referred to in Article 24, assign a Basic UDI-DI to the device and shall provide it to the UDI database together with the other core data elements. After issuance of the relevant certificate and before placing the device on the market, the manufacturer shall provide the Basic UDI-DI to the UDI database together with the other core data elements.

Electronic System for Registration of Economic Operators (Article 27)
The Commission, after consulting the MDCG, shall set up and manage an electronic system to create the single registration number referred to in Article 28 and to collate and process information that is necessary and proportionate to identify the manufacturer and, where applicable, the authorized representative and the importer. The details regarding the information should be provided to that electronic system by the economic operators. Within 2 weeks of placing a device on the market, importers shall verify what the manufacturer or authorized representative has provided to the electronic system.

Registration of Manufacturers, Authorized Representatives, and Importers (Article 28)
Before placing a device on the market, manufacturers, authorized representatives, and importers shall, in order to register, submit to the electronic system referred to in Article 30. In cases where the conformity assessment procedure requires the involvement of a notified body pursuant to Article 48, shall be provided to that electronic system before applying to the notified body. After having verified the data entered pursuant to paragraph 1, the competent authority shall obtain a single registration number ("SRN") from the electronic system referred to in Article 27 and issue it to the manufacturer, the authorized representative, or the importer. The manufacturer shall use the SRN when applying to a notified body for conformity assessment and for accessing EUDAMED in order to fulfil its obligations under Article 26.

Summary of Safety and Performance (Article 29)
The summary of safety and performance shall include at least the following aspects: (a) the identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN; (b) the intended purpose of the device and any indications, contraindications, and target populations; (c) a description of the device, including a reference to previous generation(s) or variants if such exist and a description of the differences, as well as, where relevant, a description of any accessories, other devices, and products, which are intended to be used in combination with the device; (d) reference to any harmonized standards and CS applied; (e) the summary of the performance evaluation and relevant information on the PMPF; (f) the metrological traceability of assigned values; (g) suggested profile and training

for users; and (h) information on any residual risks and any undesirable effects, warnings, and precautions.

European Database on Medical Devices (Article 30)
The Commission, after consulting the MDCG, shall set up, maintain, and manage the European database on medical devices ("EUDAMED") in accordance with the conditions and detailed arrangements established by Articles 33 and 34 of Regulation (EU) 2017/745. EUDAMED shall include the following electronic systems: (a) the electronic system for registration of devices referred to in Article 26; (b) the UDI database referred to in Article 25; (c) the electronic system on registration of economic operators referred to in Article 27; (d) the electronic system on notified bodies and on certificates referred to in Article 52; (e) the electronic system on performance studies referred to in Article 69; (f) the electronic system on vigilance and post-market surveillance referred to in Article 87; and (g) the electronic system on market surveillance referred to in Article 95.

6 Notified Bodies (Article 31–46)

Authorities Responsible for Notified Bodies
Any Member State that intends to designate a conformity assessment body as a notified body, or has designated a notified body, to carry out conformity assessment activities under this Regulation shall appoint an authority (the "authority responsible for notified bodies"), which may consist of separate constituent entities under national law and shall be responsible for setting up and carrying out the necessary procedures for the assessment, designation, and notification of conformity assessment bodies and for the monitoring of notified bodies, including subcontractors and subsidiaries of those bodies. The authority responsible for notified bodies shall be established, organized, and operated so as to safeguard the objectivity and impartiality of its activities and to avoid any conflicts of interests with conformity assessment bodies. The authority responsible for notified bodies shall safeguard the confidential aspects of the information it obtains. However, it shall exchange information on notified bodies with other Member States, the Commission, and, when required, other regulatory authorities.

Application by Conformity Assessment Bodies for Designation Conformity assessment bodies shall submit an application for designation to the authority responsible for notified bodies. The application shall specify the conformity assessment activities as defined in this Regulation, and the types of devices for which the body is applying to be designated, and shall be supported by documentation demonstrating compliance (Article 34).

Assessment of the Application The authority responsible for notified bodies shall within 30 days check that the application referred to in Article 34 is complete and shall request the applicant to provide any missing information. Once the application

is complete, that national authority shall send it to the Commission. The authority responsible for notified bodies shall review the application and supporting documentation in accordance with its own procedures and shall draw up a preliminary assessment report. The authority responsible for notified bodies shall submit the preliminary assessment report to the Commission which shall immediately transmit it to the MDCG (Article 35).

Language Requirements All documents required pursuant to Articles 34 and 35 shall be drawn up in a language or languages which shall be determined by the Member State concerned. Member States, in applying the first paragraph, shall consider accepting and using a commonly understood language in the medical field, for all or part of the documentation concerned. The Commission shall provide translations of the documentation pursuant to Articles 34 and 35, or parts thereof into an official Union language, such as is necessary for that documentation to be readily understood by the joint assessment team appointed in accordance with Article 35.

Identification Number and List of Notified Bodies The Commission shall assign an identification number to each notified body for which the notification becomes valid in accordance with Article 38. It shall assign a single identification number even when the body is notified under several Union acts. If they are successfully designated in accordance with this Regulation, bodies notified pursuant to Directive 98/79/EC shall retain the identification number assigned to them pursuant to that Directive. The Commission shall make the list of the bodies notified under this Regulation, including the identification numbers that have been assigned to them and the conformity assessment activities as defined in this Regulation and the types of devices for which they have been notified, accessible to the public in NANDO. The Commission shall ensure that the list is kept up to date.

Monitoring and re-assessment of notified bodies: Notified bodies shall, without delay, and at the latest within 15 days, inform the authority responsible for notified bodies of relevant changes which may affect their compliance or their ability to conduct the conformity assessment activities relating to the devices for which they have been designated.

Challenge to the Competence of Notified Bodies The Commission, in conjunction with the MDCG, shall investigate all cases where concerns have been brought to its attention regarding the continued fulfilment by a notified body, or of one or more of its subsidiaries or subcontractors, of the requirements or the obligations to which they are subject. It shall ensure that the relevant authority responsible for notified bodies is informed and is given an opportunity to investigate those concerns (Article 43).

Peer Review and Exchange of Experience Between Authorities Responsible for Notified Bodies

The Commission shall provide for the organization exchange of experience and coordination of administrative practice between the authorities responsible for notified bodies. Such exchange shall cover elements including:

(a) Development of best practice documents relating to the activities of the authorities responsible for notified bodies
(b) Development of guidance documents for notified bodies in relation to the implementation of this Regulation
(c) Training and qualification of the experts referred to in Article 36
(d) Monitoring of trends relating to changes to notified body designations and notifications and trends in certificate withdrawals and transfers between notified bodies
(e) Monitoring of the application and applicability of scope codes referred to in Article 38(13)
(f) Development of a mechanism for peer reviews between authorities and the Commission
(g) Methods of communication to the public on the monitoring and surveillance activities of authorities and the Commission on notified bodies

Coordination of Notified Bodies The Commission shall ensure that appropriate coordination and cooperation between notified bodies is put in place and operated in the form of the coordination group of notified bodies, as referred to in Article 49 of Regulation (EU) 2017/745. The bodies notified under this Regulation shall participate in the work of that group.

7 Classification and Conformity Assessment (Article 47–55)

Classification of Devices Devices shall be divided into classes A, B, C, and D, taking into account the intended purpose of the devices and their inherent risks. Any dispute between the manufacturer and the notified body concerned, arising from the application of Annexure, shall be referred for a decision to the competent authority of the Member State in which the manufacturer has its registered place of business. The competent authority of the Member State in which the manufacturer has its registered place of business shall notify the MDCG and the Commission of its decision. The decision shall be made available upon request. In order to ensure the uniform application of Annexure, and taking account of the relevant scientific opinions of the relevant scientific committees, the Commission may adopt implementing acts to the extent necessary to resolve issues of divergent interpretation and of practical application.

Certificates of Conformity The certificates shall be valid for the period they indicate, which shall not exceed 5 years. On application by the manufacturer, the validity of the certificate may be extended for further periods, each not exceeding 5 years, based on a re-assessment in accordance with the applicable conformity assessment procedures. Any supplement to a certificate shall remain valid as long as the certificate which it supplements is valid. Where a notified body finds that the requirements of this Regulation are no longer met by the manufacturer, it shall, taking account of the principle of proportionality, suspend or withdraw the certificate issued or impose

any restrictions on it unless compliance with such requirements is ensured by appropriate corrective action taken by the manufacturer within an appropriate deadline set by the notified body. The notified body shall give the reasons for its decision (Article 51).

Voluntary Change of Notified Body In cases where a manufacturer terminates its contract with a notified body and enters into a contract with another notified body in respect of the conformity assessment of the same device, the detailed arrangements for the change of notified body shall be clearly defined in an agreement between the manufacturer, the incoming notified body, and, where practicable, the outgoing notified body. That agreement shall cover at least the following aspects: (a) the date on which the certificates issued by the outgoing notified body become invalid; (b) the date until which the identification number of the outgoing notified body may be indicated in the information supplied by the manufacturer, including any promotional material; (c) the transfer of documents, including confidentiality aspects and property rights; (d) the date after which the conformity assessment tasks of the outgoing notified body are assigned to the incoming notified body; and (e) the last serial number or lot number for which the outgoing notified body is responsible. The outgoing notified body shall withdraw the certificates it has issued for the device concerned on the date on which they become invalid (Article 53).

Certificate of Free Sale For the purpose of export and upon request by a manufacturer or an authorized representative, the Member State in which the manufacturer or the authorized representative has its registered place of business shall issue a certificate of free sale declaring that the manufacturer or the authorized representative, as applicable, has its registered place of business on its territory and that the device in question bearing the CE marking in accordance with this Regulation may be marketed in the Union. The certificate of free sale shall set out the Basic UDI-DI of the device as provided to the UDI database under Article 26. Where a notified body has issued a certificate pursuant to Article 51, the certificate of free sale shall set out the unique number identifying the certificate issued by the notified body (Article 55).

8 Clinical Evidence, Performance Evaluation (Articles 56–77)

Performance Evaluation and Clinical Evidence Performance evaluation of a device is a continuous process by which data are assessed and analyzed to demonstrate the scientific validity, analytical performance, and clinical performance of that device for its intended purpose as stated by the manufacturer. To plan, continuously conduct, and document a performance evaluation, the manufacturer shall establish and update a performance evaluation plan. The performance evaluation plan shall specify the characteristics and the performance of the device and the pro-

cess and criteria applied to generate the necessary clinical evidence. The performance evaluation shall be thorough and objective, considering both favorable and unfavorable data. Its depth and extent shall be proportionate and appropriate to the characteristics of the device including the risks, risk class, performance, and its intended purpose. The manufacturer shall specify and justify the level of the clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose.

General Requirements Regarding Performance Studies The manufacturer shall ensure that a device for performance study complies with the general safety and performance requirements covered by the performance study and that, with regard to those aspects, every precaution has been taken to protect the health and safety of the patient, user, and other persons. Where appropriate, performance studies shall be performed in circumstances similar to the normal conditions of use of the device. Performance studies shall be designed and conducted in such a way that the rights, safety, dignity, and well-being of the subjects participating in such performance studies are protected and prevail over all other interests and the data generated are scientifically valid, reliable, and robust. Performance studies, including performance studies that use leftover samples, shall be conducted in accordance with applicable law on data protection (Article 57).

Informed Consent (Article 58) Informed consent shall be written, dated, and signed by the person performing the interview and by the subject or, where the subject is not able to give informed consent, his or her legally designated representative after having been duly informed. Where the subject is unable to write, consent may be given and recorded through appropriate alternative means in the presence of at least one impartial witness. In that case, the witness shall sign and date the informed consent document. The subject or, where the subject is not able to give informed consent, his or her legally designated representative shall be provided with a copy of the document or the record, as appropriate, by which informed consent has been given. The informed consent shall be documented. Adequate time shall be given for the subject or his or her legally designated representative to consider his or her decision to participate in the performance study. Information given to the subject or, where the subject is not able to give informed consent, his or her legally designated representative for the purposes of obtaining his or her informed consent shall:

(a) Enable the subject or his or her legally designated representative to understand:

    (i) The nature, objectives, benefits, implications, risks, and inconveniences of the performance study
    (ii) The subject's rights and guarantees regarding his or her protection, in particular his or her right to refuse to participate in and the right to withdraw from the performance study at any time without any resulting detriment and without having to provide any justification

(iii) The conditions under which the performance study is to be conducted, including the expected duration of the subject's participation in the performance study
(iv) The possible treatment alternatives, including the follow-up measures if the participation of the subject in the performance study is discontinued

(b) Be kept comprehensive, concise, clear, relevant, and understandable to the subject or his or her legally designated representative
(c) Be provided in a prior interview with a member of the investigating team who is appropriately qualified under national law
(d) Include information about the applicable damage compensation system

Performance Studies on Minors (Article 61) A performance study on minors may be conducted only where, in addition to the conditions set out in Article 58, all of the following conditions are met:

(a) The informed consent of their legally designated representative has been obtained.
(b) The minors have received the information referred to in Article 59(2) in a way adapted to their age and mental maturity and from investigators or members of the investigating team who are trained or experienced in working with children.
(c) The explicit wish of a minor who is capable of forming an opinion and assessing the information referred to in Article 59 to refuse participation in, or to withdraw from, the performance study at any time is respected by the investigator.
(d) No incentives or financial inducements are given to subjects or their legally designated representatives, except for compensation for expenses and loss of earnings directly related to the participation in the performance study.
(e) The performance study is intended to investigate treatments for a medical condition that only occurs in minors, or the performance study is essential with respect to minors to validate data obtained in performance studies on persons able to give informed consent or by other research methods.
(f) The performance study either relates directly to a medical condition from which the minor concerned suffers or is of such a nature that it can only be carried out on minors.
(g) There are scientific grounds for expecting that participation in the performance study will produce:

(i) A direct benefit to the minor subject outweighing the risks and burdens involved
(ii) Some benefit for the population represented by the minor concerned when the performance study will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the minor's condition.

(h) The minor shall take part in the informed consent procedure in a way adapted to his or her age and mental maturity.

(i) If during a performance study the minor reaches the age of legal competence to give informed consent as defined in the national law, his or her expressed informed consent shall be obtained before that subject can continue to participate in the performance study.

Performance Studies on Pregnant or Breastfeeding Women (Article 62) A performance study on pregnant or breastfeeding women may be conducted only where, in addition to the conditions set out in Article 58, all of the following conditions are met:

(a) The performance study has the potential to produce a direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, fetus, or child after birth, outweighing the risks and burdens involved.
(b) If such a performance study has no direct benefit for the pregnant or breastfeeding woman concerned, or her embryo, fetus, or child after birth, it can be conducted only if:
    (i) A performance study of comparable effectiveness cannot be carried out on women who are not pregnant or breastfeeding
    (ii) The performance study contributes to the attainment of results capable of benefitting pregnant or breastfeeding women or other women in relation to reproduction or other embryos, fetuses, or children
    (iii) The performance study poses a minimal risk to, and imposes a minimal burden on, the pregnant or breastfeeding woman concerned, her embryo, fetus, or child after birth
(c) Where research is undertaken on breastfeeding women, particular care is taken to avoid any adverse impact on the health of the child.
(d) No incentives or financial inducements are given to subjects, except for compensation for expenses and loss of earnings directly related to the participation in the performance study.

Additional national measures (Article 63): Member States may maintain additional measures regarding persons performing mandatory military service; persons deprived of liberty; persons who, due to a judicial decision, cannot take part in performance studies; or persons in residential care institutions.

Performance Studies in Emergency Situations (Article 64) (a) Due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the performance study.

(b) There are scientific grounds to expect that participation of the subject in the performance study will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition.

(c) It is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative.
(d) The investigator certifies that he or she is not aware of any objections to participate in the performance study previously expressed by the subject.
(e) The performance study relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the performance study is of such a nature that it may be conducted exclusively in emergency situations.
(f) The performance study poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition.

Damage Compensation (Article 65) Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a performance study conducted on their territory are in place in the form of insurance, a guarantee, or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.

Assessment by Member States (Article 67) Member States shall ensure that the persons validating and assessing the application, or deciding on it, do not have conflicts of interest and are independent of the sponsor, the investigators involved, and natural or legal persons financing the performance study, as well as free of any other undue influence. Member States shall ensure that the assessment is done jointly by a reasonable number of persons who collectively have the necessary qualifications and experience. Member States shall assess whether the performance study is designed in such a way that potential remaining risks to subjects or third persons, after risk minimization, are justified, when weighed against the clinical benefits to be expected.

Conduct of a Performance Study (Article 68) The sponsor and the investigator shall ensure that the performance study is conducted in accordance with the approved performance study plan. In order to verify that the rights, safety, and well-being of subjects are protected, that the reported data are reliable and robust, and that the conduct of the performance study is in compliance with the requirements of this Regulation, the sponsor shall ensure adequate monitoring of the conduct of a performance study. The extent and nature of the monitoring shall be determined by the sponsor on the basis of an assessment that takes into consideration all characteristics of the performance study including the following:

(a) The objective and methodology of the performance study
(b) The degree of deviation of the intervention from normal clinical practice

Recording and Reporting of Adverse Events That Occur During Performance Studies (Article 76) The sponsor shall fully record all of the following:

(a) Any adverse event of a type identified in the performance study plan as being critical to the evaluation of the results of that performance study
(b) Any serious adverse event
(c) Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
(d) Any new findings in relation to any event referred to in points (a) to (c)

The sponsor shall report without delay to all Member States in which a performance study is being conducted all of the following by means of the electronic system referred to in Article 69:

(a) Any serious adverse event that has a causal relationship with the device, the comparator, or the study procedure or where such causal relationship is reasonably possible
(b) Any device deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate
(c) Any new findings in relation to any event referred to in points (a) and (b)

The period for reporting shall take account of the severity of the event. Where necessary to ensure timely reporting, the sponsor may submit an initial report that is incomplete followed up by a complete report.

9 Post-market Surveillance, Vigilance, and Market Surveillance (Article 78–95)

Post-market Surveillance System of the Manufacturer For each device, manufacturers shall plan, establish, document, implement, maintain, and update a post-market surveillance system in a manner that is proportionate to the risk class and appropriate for the type of device. That system shall be an integral part of the manufacturer's quality management system referred to in Article 10. The post-market surveillance system shall be suited to actively and systematically gather, record, and analyze relevant data on the quality, performance, and safety of a device throughout its entire lifetime and draw the necessary conclusions and determine, implement, and monitor any preventive and corrective actions.

Periodic Safety Update Report (Article 81) Manufacturers of class C and class D devices shall prepare a periodic safety update report ("PSUR") for each device and where relevant for each category or group of devices summarizing the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Article 79 together with a rationale and description of any preventive and corrective actions taken. Throughout the lifetime of the device concerned, that PSUR shall set out (a) the conclusions of the

benefit-risk determination, (b) the main findings of the PMPF, and (c) the volume of sales of the device and an estimate of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device. Manufacturers of class D devices shall submit PSUR by means of the electronic system referred to in Article 87 to the notified body involved in the conformity assessment of such devices in accordance with Article 48. The notified body shall review the report and add its evaluation to that electronic system with details of any action taken. Such PSUR and the evaluation by the notified body shall be made available to competent authorities through that electronic system.

Reporting of Serious Incidents and Field Safety Corrective Actions (Article 82)
Manufacturers of devices, made available on the Union market, other than devices for performance study, shall report, to the relevant competent authorities, in accordance with Articles, the following: (a) any serious incident involving devices made available on the Union market, except expected erroneous results which are clearly documented and quantified in the product information and in the technical documentation and are subject to trend reporting pursuant to Article 83; and (b) any field safety corrective action in respect of devices made available on the Union market, including any field safety corrective action undertaken in a third country in relation to a device which is also legally made available on the Union market, if the reason for the field safety corrective action is not limited to the device made available in the third country.

Manufacturers shall report any serious incident as referred to in point (a) immediately after they have established a causal relationship between that incident and their device or that such causal relationship is reasonably possible, and not later than 15 days after they become aware of the incident. In the event of death or an unanticipated serious deterioration in a person's state of health, the report shall be provided immediately after the manufacturer has established or as soon as it suspects a causal relationship between the device and the serious incident but not later than 10 days after the date on which the manufacturer becomes aware of the serious incident.

Analysis of Vigilance Data (Article 85) The Commission shall, in collaboration with the Member States, put in place systems and processes to actively monitor the data available in the electronic system referred to in Article 87, in order to identify trends, patterns, or signals in the data that may reveal new risks or safety concerns. Where a previously unknown risk is identified or the frequency of an anticipated risk significantly and adversely changes the benefit-risk determination, the competent authority or, where appropriate, the coordinating competent authority shall inform the manufacturer or where applicable the authorized representative, which shall then take the necessary corrective actions.

Market Surveillance Activities (Article 88) The competent authorities shall perform appropriate checks on the conformity characteristics and performance of devices including, where appropriate, a review of documentation and physical or laboratory checks on the basis of adequate samples. The competent authorities

shall, in particular, take account of established principles regarding risk assessment and risk management, vigilance data, and complaints. The competent authorities shall draw up annual surveillance activity plans and allocate a sufficient number of material and competent human resources in order to carry out those activities taking into account the European market surveillance program developed by the MDCG pursuant to Article 99 and local circumstances.

Evaluation of Devices Suspected of Presenting an Unacceptable Risk or Other Non-compliance (Article 89) Where the competent authorities of a Member State, based on data obtained by vigilance or market surveillance activities or on other information, have reason to believe that a device:

(a) May present an unacceptable risk to the health or safety of patients, users, or other persons, or to other aspects of the protection of public health.
(b) Otherwise does not comply with the requirements laid down in this Regulation, they shall carry out an evaluation of the device concerned covering all requirements laid down in this Regulation relating to the risk presented by the device or to any other non-compliance of the device.

Good Administrative Practice (Article 94) Where such a measure is addressed to a specific economic operator, the competent authority shall notify without delay the economic operator concerned of that measure and shall at the same time inform that economic operator of the remedies available under the law or the administrative practice of the Member State concerned and of the time limits to which such remedies are subject. Where the measure is of general applicability, it shall be appropriately published. Except in cases where immediate action is necessary for reasons of unacceptable risk to human health or safety, the economic operator concerned shall be given the opportunity to make submissions to the competent authority within an appropriate period of time that is clearly defined before any measure is adopted.

10 EU Reference Laboratories and Device Registers (Articles 96–101)

Competent Authorities (Article 96) The Member States shall designate the competent authority or authorities responsible for the implementation of this Regulation. They shall entrust their authorities with the powers, resources, equipment, and knowledge necessary for the proper performance of their tasks pursuant to this Regulation. The Member States shall communicate the names and contact details of the competent authorities to the Commission which shall publish a list of competent authorities.

Cooperation (Article 97) The competent authorities of the Member States shall cooperate with each other and with the Commission. The Commission shall provide for the organization of exchanges of information necessary to enable this Regulation to be

applied uniformly. Member States shall with the support of the Commission participate, where appropriate, in initiatives developed at international level with the aim of ensuring cooperation between regulatory authorities in the field of medical devices.

Medical Device Coordination Group (Article 98) The Medical Device Coordination Group (MDCG) established in accordance with the conditions and detailed arrangements referred to in Article 103 and 107 of Regulation (EU) 2017/745 shall carry out, with the support of the Commission as provided in Article 104 of Regulation (EU) 2017/745, the tasks conferred on it under this Regulation as well as those under Regulation (EU) 2017/745.

Tasks of the MDCG (Article 99) Under this Regulation, the MDCG shall have the following tasks: (a) to contribute to the assessment of applicant conformity assessment bodies; (b) to advise the Commission, at its request, in matters concerning the coordination group of notified bodies as established pursuant to Article 45; (c) to contribute to the development of guidance aimed at ensuring effective and harmonized implementation of this Regulation, in particular regarding the designation and monitoring of notified bodies, application of the general safety and performance requirements, and conduct of performance evaluations by manufacturers, assessment by notified bodies, and vigilance activities; (d) to contribute to the development of device standards and of CS; (e) to assist the competent authorities of the Member States in their coordination activities in particular in the fields of classification and the determination of the regulatory status of devices, performance studies, vigilance, and market surveillance including the development and maintenance of a framework for a European market surveillance program with the objective of achieving efficiency and harmonization of market surveillance in the Union, in accordance with Article 88; (f) to provide advice, either on its own initiative or at request of the Commission, in the assessment of any issue related to the implementation of this Regulation; and (g) to contribute to harmonized administrative practice with regard to devices in the Member States.

Device Registers and Databanks (Article 101) The Commission and the Member States shall take all appropriate measures to encourage the establishment of registers and databanks for specific types of device setting common principles to collect comparable information. Such registers and databanks shall contribute to the independent evaluation of the long-term safety and performance of devices.

11 Confidentiality, Data Protection, Funding, and Penalties (Articles 102–106)

Confidentiality (Article 102) Unless otherwise provided for in this Regulation and without prejudice to existing national provisions and practices in the Member States on confidentiality, all parties involved in the application of this Regulation shall respect the confidentiality of information and data obtained in carrying out their tasks in order to protect the following:

(a) Commercially confidential information and trade secrets of a natural or legal person, including intellectual property rights unless disclosure is in the public interest
(b) The effective implementation of this Regulation, in particular for the purpose of inspections, investigations, or audits

Data Protection (Article 103) Member States shall apply Directive 95/46/EC to the processing of personal data carried out in the Member States pursuant to this Regulation. Regulation (EC) No 45/2001 shall apply to the processing of personal data carried out by the Commission pursuant to this Regulation.

Levying of Fees (Article 104) This Regulation shall be without prejudice to the possibility for Member States to levy fees for the activities set out in this Regulation, provided that the level of the fees is set in a transparent manner and on the basis of cost-recovery principles. Member States shall inform the Commission and the other Member States at least 3 months before the structure and level of fees are to be adopted. The structure and level of fees shall be made publicly available on request.

Funding of Activities Related to Designation and Monitoring of Notified Bodies (Article 105) The costs associated with joint assessment activities shall be covered by the Commission. The Commission shall, by means of implementing acts, lay down the scale and structure of recoverable costs and other necessary implementing rules. Those implementing acts shall be adopted in accordance with the examination procedure referred to in Article 107(3).

Penalties (Article 106) The Member States shall lay down the rules on penalties applicable for infringement of the provisions of this Regulation and shall take all measures necessary to ensure that they are implemented. The penalties provided for shall be effective, proportionate, and dissuasive.

Annexure

Device Classification Rules

Rule 1: Devices intended to be used for the following purposes are classified as class D:

- Detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues, or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation, or cell administration
- Detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation;
- Determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management

Rule 2: Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue, or

organs that are intended for transfusion or transplantation or cell administration, are classified as class C.

Rule 3: Devices are classified as class C if they are intended:

(a) For detecting the presence of, or exposure to, a sexually transmitted agent
(b) For detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation
(c) For detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, fetus, or embryo being tested, or to the individual's offspring
(d) For prenatal screening of women in order to determine their immune status toward transmissible agents
(e) For determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring
(f) To be used as companion diagnostics
(g) To be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring
(h) To be used in screening, diagnosis, or staging of cancer
(i) For human genetic testing
(j) For monitoring of levels of medicinal products, substances, or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring
(k) For management of patients suffering from a life-threatening disease or condition
(l) For screening for congenital disorders in the embryo or fetus
(m) For screening for congenital disorders in newborn babies where failure to detect and treat such disorders could lead to life-threatening situations or severe disabilities

Rule 4: (a) Devices intended for self-testing are classified as class C, except for devices for the detection of pregnancy, for fertility testing, and for determining cholesterol level and devices for the detection of glucose, erythrocytes, leucocytes, and bacteria in urine, which are classified as class B. (b) Devices intended for near-patient testing are classified in their own right.

Rule 5: The following devices are classified as class A: (a) products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination; (b) instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures; and (c) specimen receptacles.

Reference

Regulation (EU) 2017/746 ofThe European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU, Official Journal of the European Union.

Device Regulations of Other Countries

Karnika Singh

1 Introduction

This chapter covers medical device regulation from several countries listed below:

1. India Medical Device regulations
2. China Medical Device regulations
3. Canada Medical Device regulations
4. New Zealand Medical Device regulations
5. Australia Medical Device regulations
6. Japan Medical Device regulations
7. Singapore Medical Device regulations
8. United Kingdom Medical Device regulations
9. European Medical Device regulations

The medical device regulations of these countries are similar in many aspects to that of the United States. However, they differ in a lot of areas as highlighted in each section.

1. **India Medical Device Regulations**

The medical device regulations came into existence in India in the year 2017 (Ministry of Health and Family Welfare Notification No. G.S.R, 78(E) dated 31 January 2017 notifies Medical Devices Rules 2017). Certain medical devices and in vitro diagnostic devices belonging to risk class B and C are included in the regulation. New devices are regularly added to this list by the Ministry of Health and Family Welfare. Since India imports most of its medical devices, the CDSCO (Central Drugs Standard Control Organization) has Central Licensing Authority (CLA) and State Licensing Authority (SLA) which are responsible for licensing to

K. Singh (✉)
The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2_18

import, manufacture for sale or for distribution and sale, stock, exhibit, or offer for sale. CLA does licensing for all import devices and Class C and Class D medical devices manufacturing, loan, and wholesale licenses. CLA may take services of a notified body to examine the manufacturing site of Class C and Class D medical devices and technical review. SLA is responsible for the manufacturing, loan, and wholesale licenses of Class A and Class B medical devices. SLA selects and authorizes a notified body to validate the requirements of quality management system and technical review for Class A and Class B medical device manufacturers.

Regulated imported medical devices that have obtained prior approval in the United States, the European Union (EU), Canada, Japan, or Australia may legally be sold in India by obtaining the necessary license which would cause a limited conformity assessment process. In such cases, the applications should accompany all documentation used in support of prior approvals. It is advised to foreign manufacturers that they must appoint an importer, holding a valid wholesale license, and would also submit a device registration application and dossier to the CLA.

1.1 Steps to Import Medical Devices in India

In order to import medical devices in India, first, the device is assigned a risk class (A, low risk; B, low–moderate high risk; C, moderate high risk; D, high risk). Then, an application of licensing needs to be filed through the online portal of Ministry of Health and Family Welfare (SUGAM). After this, the CLA may schedule an inspection of the manufacturing site. If the device under consideration has a prior approval from countries like the United States, Canada, Japan, EU, and Australia, then the license is granted. However, if that is not the case, then class A and B devices are evaluated for their safety and performance based on the published data or the clinical investigation that was carried out in the respective country. For class C and D devices, the same is established by conducting clinical investigation by India itself before the granting of license.

1.2 Steps to Manufacture Medical Devices for Sale or for Distribution

The first few steps until filing an application are same as above. Once the applications are received, they are examined by the SLA or CLA already defined. The SLA can provide the license to the applicant and then schedule for a technical review and onsite audit or vice versa. The CLA however will always grant the license after the technical review and onsite audit.

2 China Medical Device Regulations

The medical device regulations in China are controlled by NMPA (National Medical Products Administration) formally known as the China Food and Drug Administration (CFDA). It classifies devices in risk categories, I, II, and III, ranging from low to high. China follows the following criteria to classify medical devices into the abovementioned three classes:

- Class I: those devices whose safety and effectiveness can be ensured through routine administration.
- Class II: the devices which would need additional control to establish their safety and effectiveness.
- Class III: these include devices which are used for life support and/or implanted into the body and therefore may be a major threat to patient's health.

In order to register medical devices in China, which are not manufactured in the country, the respective company has to provide device samples to NMPA. In the case of class II and III devices, it is mandatory for the manufacturer to send applicable documents stating that the device has been approved in its manufacturing country. Examples of such documents include CE Mark, 510(k) letter, ISO 13485 certification, approved Premarket Approval Application, etc. The application may also require providing supporting clinical data associated with the device. All the product information on the packaging label of the device should be translated to simplified Chinese. Once approved, the medical device registration in China is valid for 5 years (as opposed to 4 years). For renewal of registration, the renewal application should be submitted to the same department 6 months prior to the expiration of previous application. It is required by the outside manufacturers to hire China-based agents to represent their interests. Such agents would be responsible for proving technical service, maintenance support for the device, recall assistance, supervising the registration process, and providing support for the manufacturer in the case of an adverse event of device malfunction. The manufacturer will provide all their details (name, address, contact information, etc.) to the designated agent in the registration application.

In the year 2017, NMPA amended the medical device regulations, and in 2018, a revised draft was published. Some significant changes are outlined below:

- Unique Data Identification (UDI): The purpose of UDI is to monitor the medical devices by allowing their tracking from the manufacturing point to their distribution and use. The information to be stored in the UDI database includes the expiry and production dates of the device, the device model, and the UDI code.
- Market Authorization Holder (MAH): The MAH has to ensure the quality of their products and that they meet all applicable requirements, submit yearly self-inspection reports to respective authorities, and regularly update their products' information in the NMPA's UDI.
- Clinical Trial Management System: The clinical evaluation is not mandatory for class I and most class II devices. In order for class III devices to skip the clinical

evaluation, they should have a proven safety record. The NMPA would review the clinical data from foreign countries. All high-risk devices and devices for life support would have to be evaluated in China.
- Prioritization of innovative devices: Foreign manufacturers would be allowed to import "innovative" medical devices into China without any approval certificates.

3 Canada Medical Device Regulations

The Medical Device Regulations of Canada apply to sale, advertising and import of a medical device for sale to the general public as opposed to personal use. These regulations also apply on in vitro diagnostic products (could be a drug or contains a drug). The Canada medical device regulations also classify the devices according to risk levels. Class I is the lowest risk, and class IV is the highest risk. It should be noted that a device could be classified into more than one class; in this case, the highest classification would apply.

3.1 General

It is the manufacturer's responsibility to ensure that the medical device meets all the relevant requirements.

Safety and effectiveness requirement: The manufacturer has to identify all the inherent risks of the device, eliminate them if possible or reduce them to an acceptable level, and provide protection guidelines from those risks. The manufacturer has to also provide the information about the remaining risks with the device. The manufacturer has to minimize the hazard arising from potential failures of the device during its usage. The characteristic and performance of the medical device should not decrease under regular use such that the health and safety of the patient are compromised. The transport and storage conditions of the device should not adversely affect the medical device. The materials used in the device should complement each other so that it does not pose a risk to the patient. The design, manufacture, and packaging of the device should minimize any hazards like flammability, contamination, radiation, leakage, and electric hazards. If a medical device is supposed to be sterile, then they should be manufactured in sterile conditions and sterilized by a validated method. A measuring device should function within the tolerance limits suitable for the medical conditions and other intended purposes. For software-based devices, software would be designed keeping the intended performance in mind and validated regularly.

Labeling Requirements The import and selling of a medical device is not permitted until the labeling requirements are met. The label shall contain the name of the

device, details of the manufacturer, all the identifying information, control number for high-risk devices, details about the package contents, indication of sterility, expiry date or best before date, directions for use, performance specifications, and storage conditions. All the labeling has to be legit and easily understandable to the user. In case of absence of a label in the imported device, a prior notice has to be sent to the Minister. Before selling the medical device, it should be relabeled within 3 months of importation according to these regulations. The Minister needs to be notified in writing about who is going to relabel the product in Canada. The labeling has to be done in at least two languages (English and French). Other labeling requirements are similar to those outlined in ISO 16061.

Contraceptive Devices: Advertising A condom can be sold as long as it is marketed as a device for preventing sexually transmitted diseases (STDs), and the label of the condom should specify the same. Contraceptive devices except intrauterine devices (IUDs) can be advertised publicly but may not utilize door-to-door distribution or mail as a means of advertising.

Class I Medical Devices The minister reserves the right to ask for more information in order to approve a class I medical device.

Class II, III, and IV Medical Devices

Prohibition: These devices require a license to import or sell and advertise. The advertisement has to clearly contain the warning, "may not have been licensed in accordance with the Canadian law."

Medical Devices Deemed Licensed: For a licensed system, all its parts are considered licensed for import, sale, and advertisement. In case of a test kit, all its reagents are licensed for import, sale, and advertisement. If a licensed medical device is a part of a medical device group, that group is deemed licensed for import, sale, and advertisement and vice versa.

Application for a Medical Device License: The application for license has to be submitted to the Minister in the format decided by the Minister. It would contain the name, class, and identifier of the device, manufacturer details, and establishment where the device is manufactured.

The application for class II device would have additional details like medical conditions for which the device would be used for, list of applicable standards attested by a senior official, and copy of device label, and the in vitro diagnostic device would have to be attested by a senior official that it has undergone investigational testing on human subjects representing intended users, with a copy of the quality management system certificate indicating that it satisfies National Standard of Canada CAN/CSA-ISO 13485:2016, Medical devices – Quality management systems – Requirements for regulatory purposes.

The license application for class III devices would additionally include list of countries other than Canada where the device has been sold with all the details of the sale (units sold, problems during sale, etc.), risk assessment, quality plan, details

of the materials used in the device, the manufacturing process, a list of validation studies (preclinical and clinical, process validation, software validation, etc.), evidence of the biological safety of the device, bibliography of all the reports about the use, and safety and effectiveness of the device.

Quality Management System Certificate: This would be taken care of by an appropriately qualified person appointed by the Minister. This certificate is valid for 3 years at most. The Minister has to be notified in writing by the registrar about suspending or cancelling a certificate. Also he will notify the Minister within 15 days of expiration if the certificate is not renewed. The Minister reserved the right to fire or reinstate the registrar under certain conditions.

Foreign Manufacturers: If the foreign manufacturer were from a country that has a regulatory authority recognized by the minister, then this would allow for exemption in the submission of abovementioned documents. The application needs to contain a certificate of compliance and a summary report issued by the regulatory body of that country. The Minister can recognize a regulatory authority of a foreign country if it is able to establish that the device meets all the applicable requirements. The Minister can also provide the list of recognized regulatory authorities of foreign countries upon request.

Application for a Medical Device License Amendment: The Minister would approve any amendments like:

(a) A significant change in the application for class III or IV device
(b) A change that would influence the class of device
(c) Change in manufacturer's name
(d) Change in name of device
(e) Change in the device identifier
(f) Changes in the medical conditions, purposes or uses, or selling criteria of a class II device

Additional Information and Samples: The minister may request for additional documentation if he is not able to reach a decision about the application. This additional information may also be requesting device samples.

Issuance: If the application meets all the requirements, the Minister shall issue a medical device license or amend the license of the manufacture. The license holder would then have to comply with the terms and conditions of the license.

Refusal to Issue: If the applicant does not comply with the regulations or supplied false information, it may lead to refusal of a medical device license or amendment. The Minister shall inform the applicant in writing and provide an applicant with an opportunity to be heard.

Suspension: The following conditions would lead to suspension of the device license: any contradiction of the regulations, supplying misleading information in the application, failure to comply with the terms and conditions of the license, failure to provide the extra information/materials requested by the Minister, cessation of meeting requirements, and any future information obtained after the granting of license in terms of quality, manufacturing, etc. The Minister would

consider the licensee's history of compliance with the regulations and risk that would be caused if the license were continued. The minister shall wait to suspend the license until he informs the licensee in writing the reason of suspension and any corrective measures that may be required with the time limit. The licensee would be given an opportunity to be heard. However, if the risk were big such that patients and people using the device would be at a health risk, then the licensee would not be heard. The licensee holds the rights to appeal a reconsideration of suspension to the Minister in writing. The Minister will then have 45 days for hearing the licensee. The minister may reinstate the license if the corrective measures have been taken or the basis of suspension is unjustified.

Obligation to Inform: The license holder shall inform the Minister in an authorized form, before November 1, that all documents supplied by the manufacturer are still valid or have changed since last time. Failure to do this may result in suspension. If the licensee decides to discontinue the sale of the device in Canada, then he has to inform the Minister within 30 days of discontinuation, and the license would be cancelled.

Obligation to submit certificate: The manufacturer has to submit a copy of new or modified quality management system certificate to the Minister within 30 days of issuance.

Disclosure of Information in Respect of Clinical Studies or Investigational Testing: This is in regard to the application for class III or IV medical devices. The details of the clinical study or investigational testing have to be disclosed if the Minister issues a license under conditions discussed under "issuance." However, if this information was provided as a supporting material or contains methods exclusive to the manufacturer, then they need not be revealed. The Minister can divulge this information without the consent of the manufacturer.

Establishment License

Prohibition: Nobody can import or sell a medical device without an establishment license. This does not apply to a retailer; healthcare facility; manufacturer of a class II, III, or IV device; and a class I device manufacturer if he imports or distributes the device through someone with an establishment license.

Application: The application for the establishment license would be submitted to the Minister and contain the name and address of the establishment, details of the establishment, if the establishment is for importation or distribution, manufacturer details, medical specifications of the device, classes of the device, attestation by a senior official of the establishment that their establishment has procedures in place for distribution records, complaint holding, recalls, problem reporting, handling, storage, delivery, installation, corrective action, and servicing. The address of each building where the above procedures are carried out would also be included.

Issuance: The license would be issued by the Minister if he determines that all application requirements are met.

Annual Review of License: The review of the licenser would be submitted before April 1 every year and include all the documents in application. The review

application would be evaluated by the Minister based on the information provided.

Refusal: In an event of incorrect information or other reasonable grounds that may pose a risk to the safety of the users, the Minister would refuse to issue the license. The Minister has to notify the applicant in writing and give him the opportunity to be heard.

Suspension: The suspension requirements for establishment license are the same as for device license.

Cancellation: If the license has remained suspended for 12 months or the licensee has failed to submit a review application, then their license is subjected to cancellation.

3.2 Distribution Records

The manufacturer, importer, and distributer of a medical device would maintain distribution records for each device. Retailers and healthcare facilities may not have to maintain such records. The distribution record will contain enough information to permit complete and quick withdrawal of the medical device from the market. In the case of implants, the distribution records shall contain the information on the implant registration cards. The manufacturer would regularly update this information as per healthcare facility or the patient. The manufacturer, importer, and distributer have to retain this information for the useful life of the device and 2 years after the shipping of device. These records would be maintained in a way that they can be retrieved timely.

3.3 Complaint Handling

The manufacturer, importer, and distributer would maintain records of any reported problems regarding safety and device performance, consumer complaints, and actions taken by the manufacturer, importer, and distributer to these problems. Retailers and healthcare facilities are exempted from this as well. The manufacturer, importer, and distributer would establish and document procedures that would lead to an effective and timely investigation of the problem as well as recall of the device if needed.

3.4 Mandatory Problem Reporting

The manufacturer would make a preliminary report and a final report for the Minister, for any incident that is sold in Canada. This would include failure of the device or a decrease in its effectiveness, faulty labeling, incomplete information, etc. If this incompetence has led to the death or serious injury to the user, then this would also be reported. The preliminary report is submitted within 10 days of a serious incident and within 30 days of a minor incident. It would contain all the information about the device indicated in earlier sections, the manufacturer details, and the importer details if applicable. The date the incident was reported, details associated with the incident, contact information of the person who reported the incident, identity of the device in question, and a statement indicating whether a similar report has been made to the Minister before with details should also be included.

The final report would contain description of the incident, number of people who experienced deleterious effects to their health or have died, an elaborate explanation of the cause of incident and actions that were taken toward the incident with proper justification, actions taken after the investigation of the incident like increased post-market surveillance, corrective and preventive action with respect to the design and manufacture of the device, and device recall. The importer can submit the reports on behalf of the manufacturer with his consent. Their reports however should be identical, and the Minister should be informed about this arrangement.

3.5 Recall

The Minister shall be given the following information before any recall: details of the device (name, identifier, etc.); contact of the manufacturer, importer, and the establishment; reason for recall and associated details; assessment of the associated risk with the reported problems; the number of affected units (totaling those manufactured, imported, and sold in Canada); time period during which the affected units were circulated in Canada; name of the people to whom the device was sold; copy of recall communication; strategy planned for conducting the recall (beginning date, procedure for keeping the Minister up to date on the progress); action to prevent the recurrence of the problem; and contact information of the representative (of the manufacturer or the importer) that would answer to all recall-related questions.

The manufacturer and importer of the device would report to the Minister after the completion of recall with the results and action taken to prevent the problem from occurring again. The importer can do the submission on the manufacturer's behalf as long as they are identical and would inform the Minister of the same.

3.6 Implant Registration

The manufacturer shall provide tow implant registration cards with the implant that would contain the details of the manufacturer and the person designated by the manufacturer for collecting implant registration information; a notice informing the patient that the purpose of the card is to allow the manufacture to advise the patient of new information regarding safety, effectiveness, or performance of the implant and any corrective action required; and statement telling the patient to notify the manufacturer of an address change. An implant registration card would contain the following information: device details, details of the healthcare professional who did the implant procedure, date the device was implanted, details of the healthcare facility, and patient details. The card would be printed in both official languages and can be a total of four (two in each language). The staff member of the healthcare facility shall fill out the card immediately after the procedure and give one card to the patient and the other to the manufacturer. Patient's personal details would not be entered on the card forwarded to the manufacturer without consent of the patient or unless required by law. The manufacturer can ask the minister in writing to use an alternative method for device registration other than the cards described above. If the Minister feels that the alternate method can achieve the same goals as the cards then he can authorize this method.

3.7 Custom-Made Devices and Medical Devices to Be Imported or Sold for Special Access

Application

In this section, special access means access to medical devices that would be available for emergency use when all other traditional therapies have failed.

General

The Minister would authorize the import and sale of a class III or IV custom-made medical device for special access.

Authorization

The details of the application would include details of the device; number of requested units; manufacturer/importer details; contact of the representative; diagnosis, treatment, or prevention for which the device would be used; statement

containing the reasons why the device was chosen for the respective condition and its risk and benefits; details of the healthcare facility where the device would be used; safety and effectiveness of the device; written statement by the healthcare professional that he would inform the patient about the risks and benefits of the device; directions for use if required; and in the case of a custom-made device, "a copy of the healthcare professional's written order to the manufacturer giving the design characteristics of the device."

The Minister would authorize the device if he establishes that the benefits provided to the patients by the device outweigh the associated risks, health and safety of the patient is not compromised, there is no alternative device available in the country, and the authorization of the device would not be misused by the manufacturer or the importer to bypass the previous requirements for general devices. The issued authorization shall point out the number of units authorized for importing, number of units authorized for selling, and details of the healthcare professional to which the device would be sold.

Additional Information

The Minister may request any additional information necessary for authorization or even after authorization. The minister may cancel the authorization if he feels that the conditions for authorization are no longer being met or requested information is not submitted.

Labeling

The label of the custom-made device shall contain the name of the manufacturer and name of the device and indicate if the device is custom made or being imported or sold for special access.

Distribution Records

The manufacturer or importer is expected to maintain the distribution records of these devices in a similar manner as described before.

Reporting an Incident

The healthcare professional shall report the incident within 72 h of its occurrence with the same regulations described above.

Implant Registration

Same rules apply as above for the registration of special access devices.

3.8 Medical Devices for Investigational Testing Involving Human Subjects

General

A manufacturer or importer may sell the device (class II, III, or IV) to a qualified investigator to carry out investigational testing if the manufacturer or importers have an issued authorization and have records containing the necessary information described below.

Records

The records would contain the following information: details of the manufacturer and importer, device details, materials used in its manufacture and packaging, features of the device that allow it to be used for the respective medical condition, list of countries other than Canada where the device has been sold and the details of the sale, risk assessment and the risk reduction measures taken during the investigational testing, names of potential investigators to whom the device would be sold, institutional details where the testing would be conducted, protocol of the testing with details about device units required, hypothesis of the study, time period of the study, the patient consent form, copy of device label, and a written undertaking from each investigator; to conduct the investigational test by the protocol, inform the enrolled patient about any potential risks and benefits associated with the device, do not allow the use of the device by personnel other than the investigator, and report any incident that might happen during the study within 72 h of its occurrence.

Authorization

A written application would be submitted to the Minister for authorization. The Minister would issue the authorization if he feels that the device can be used for investigational testing without affecting the safety of the patients, investigational testing takes care of the best interests of enrolled patients, and that the objective of the testing would be achieved. The authorization shall specify the name of the qualified investigator to whom the device would be sold, kind of diagnosis or treatment for which the device would be sold, number of units authorized for selling, and the protocol for the authorized investigational testing.

Additional Information

The Minister may request additional information if he feels the need for it. The conditions that may prompt this request are as follows: if the testing can seriously endanger the health and safety of the patients, the testing contradicts the best interest of the patients, the objective of the testing may not be achieved, the investigator is not respecting the undertaking, and submission of false or misleading information. If there is failure of submission of the above documents or if the Minister identifies some problem with the submission, then he would notify the applicant in writing with explanation to either stop the sale of the device or cancel their authorization.

Labeling

The device label would contain the name of the manufacturer and the name of the device. The statements "investigational device" and "to be used by qualified investigators only" in English and in French would be indicated on the device. In case of IVDD (In Vitro Diagnostic Device), the statement "The performance specifications of this device have not been established" would be written in English and French.

Advertising

Only the person who is authorized for importing and selling the medical device for investigational testing can advertise it. The advertising has to clearly indicate that the device is for investigational testing purposes.

Other Requirements

Maintenance of distribution records, complaint handling, mandatory problem reporting, recalls, and implant registration requirements are the same as described above in previous sections.

4 New Zealand Medical Device Regulations

4.1 Legislation

The Medicines Act 1981 and its Regulations define the governing principles for the supply of medical devices in New Zealand. If other regulations apply on the device, then they need to be complied. The supplier has to ensure that their products comply with all the legislations.

4.2 Medicines Act 1981

It specifies the legal definitions for therapeutic purpose, medical device, and medicine. It defines the requirements for advertising and institutes the penalties for breaches of the Act. The key sections of the Act are:

- Interpretation
- Meaning of medical device
- Meaning of therapeutic purpose
- Powers of the Minister to prohibit imports, etc. of medicines
- Restrictions on the sale of medical devices
- Compliance with standards
- Medical advertisements
- Enforcement
- Miscellaneous provisions

- Interpretation: This section outlines the meaning of terms used throughout the act. These terms essentially have similar meanings to those described for the United States and other countries. It is suggested to go through the Medicines Act 1981 for further reading.
- Meaning of medical device: In this act, a medical device means any device, instrument, apparatus, appliance, or other article that is intended for use in humans for therapeutic purposes and not by any pharmacological, immunological, or metabolic means. The medical device would include a material that achieves the abovementioned goals. The medical device would also include anything that is going to be used with the device.
- Meaning of therapeutic purpose: This means the medical device should prevent, diagnose, monitor, alleviate, treat, cure, or compensate for a disease, ailment, defect, or injury. It should influence, inhibit, or modify a physiological process. The device has to test the susceptibility of person to a disease or ailment or influence, control, or prevent conception or test for pregnancy or investigate, replace, or modify parts of the human anatomy.
- Powers of the Minister to prohibit import, etc. of medicines: The Minister may prohibit the import, manufacture, packing, sale, possession, supply,

administration, or other use of medicines or medical devices by giving a notice in the *Gazette*. This prohibition may be permanent or conditional (not exceeding 1 year), but the Minister can exercise this power only once. He has to inform any concerned person in writing about his reasons of prohibition. It is an offence if a person goes against this Act.

- Restrictions on the sale of medical devices: The Director-General can deem a device to be unsafe and inform the importer or manufacturer in writing with his reasons. The importer or the manufacturer would have to satisfy the Director-General in return that the device is safe. They would have 45 days to send their reply from the date of notice. The Director-General may request for more evidence if he is not satisfied with those provided. If the Director-General has not questioned the safety of the device, then it should not be assumed that the device is safe as any new information may prompt him to do so. If there is an offence reported against more than two devices that they are of the same kind, then they would be considered the same until otherwise proven. If a seller fails to comply with the Director-General's request and sells the medical device or starts selling the medical device before receiving a positive notification from the Director-General, then the offending person is liable to imprisonment for up to 6 months or a fine of $5000.
- Compliance with standards: The medical device and all its components (materials and medicine it comes with, etc.) would need to comply with the standard. The seller has to clearly inform the purchaser if the device that he is buying is different from what the standard is defined for. The following things would deem a medical device to deviate from the standard: (a) any addition that is not permitted by the regulations, (b) the quantity of the addition is greater or more than permitted, and (c) the addition does not comply with the standard that is defined for that purpose. It is an offence to disregard the compliance of the standards.
- Medical advertisements: The advertisement of a medical device is prohibited if it conveys the opposite of what the device is intended for. Any advertisement that leaves out the name or description of the device, words required to be included by the regulation, or statement required by the law is not permitted.
- The advertisement that contains statement prohibited by the law or is either false or misleading is not permitted. The advertisement should directly state or imply that the medical device is not harmful or for addiction. The advertisement on TV has to have clear legit letters and should air for sufficient time to be read by the viewer. The advertisement would be considered misleading if it conveys the wrong purpose of the medical device, does not clearly tell the safety of the device, and adds purpose/effects to the medical device it is not designed for. It is an offence to create misleading advertisements for medical devices under this Act.
- Enforcement: The officer has similar power as in the United States or Canada to directly supervise medical devices. They can perform surprise inspections of the establishment where the device is being manufactured, examine any packages containing the device, oversee the manufacturing process, collect samples of the

device, check the related documents, seize any item, take photographs of articles and establishment, etc.
- Miscellaneous provisions: When any person other than the manufacturer requests for a sample of the device, they would need to put in a written request, specify the purpose of analysis, and pay the cost of the sample. Then an officer would submit it for analysis unless he believes that request is false or a hoax.

5 Australia Medical Device Regulations

The Australian Therapeutic Goods Administration (TGA) is the regulatory authority in Australia, which takes care of the therapeutic goods regulations in the country. Medical devices are categorized under therapeutic goods in this country and follow the Therapeutic Goods (Medical Devices) Regulations 2002. These regulations are similar to any other country that we have discussed in this chapter. Therefore, here, we would discuss the Australian Regulatory Guidelines for Medical Devices (ARGMD). These regulations are currently under review by the Australian government, so the version discussed here is soon to be superseded by the new one. The ARGMD gives information about the import, export, and supply of medical devices within Australia. It also describes the legislative requirements that control medical devices.

5.1 The Regulation of Medical Devices

There were approximately 36000 entries of medical devices in the Australian Register of Therapeutic Goods (ARTG) on July 1, 2011, but today, it may contain around 1 million devices. The TGA takes a risk-based approach toward regulating medical devices. The amount of regulation depends on the "intended purpose" of the device; amount of risk associated with the device in regard to the patient, the user, and other surrounding people; and internal or external use of the device and the period of use.

5.2 The Medical Device Classification System

Medical device classifications	Examples
Class I	Elastic bandages, tongue depressors, cervical collard, slings, nonsterile dressings
Class IIa	X-ray films, intravenous tubing, contact lenses, catheters
Class IIb	Blood bags, dressings for severe wounds, condoms

Medical device classifications	Examples
Class III	Coronary artery probes, intrauterine contraceptive devices, medical devices that contain medicines, such as dressings with an antimicrobial agent
Active implantable medical devices	Pacemakers, cochlear implants

5.3 Conformity Assessment and ARTG Inclusion

For ARTG inclusion, the manufacturer may use different conformity assessment procedures according to the risk classification of a device in order to show the safety, quality, and performance of a device. All devices have to go through conformity assessment except the nonsterile class I devices and those without a measuring function. However, the lower-risk devices face regulation after ARTG inclusion as opposed to higher-risk devices, which are subjected to extensive regulation before ARTG inclusion.

5.4 Medical Device Inclusion Process

The medical device inclusion process has the following steps:

Step 1 – Identify if the product needs ARTG inclusion.
Step 2 – Examine certain things before application.

- Kind of medical device, including IVD (In Vitro Diagnostics) medical device
- Manufacturer evidence for a medical device or IVD medical device
- Classification of medical device or IVD medical device
- Priority review designation
- Supporting documentation for inclusion of a medical device or IVD medical device, in the ARTG
- Auditing of applications for ARTG inclusion of a medical device or IVD medical device in the ARTG

Step 3 – Enter the TGA Business Services system (TBS).
Step 4 – Submit an application in TBS for Class I nonsterile, non-measuring, and Class 1 IVD medical devices.
Step 5 – Submit an application in TBS for Class I Medical Device (Export Only) and Class I IVD medical device (Export Only).
Step 6 – Submit an application in TBS (for all classes except Class I nonsterile, non-measuring medical device, Class 1 IVD medical device, and Class I medical device/Class I IVD medical device Export Only)
Step 7 – Processing of application

Step 8 – Printing the ARTG certificate of inclusion

5.5 Declaration of Conformity Templates (Medical Devices)

The manufacturer has to make a declaration of conformity that confirms that the device complies with the applicable provisions of the essential principles, classification rules, and relevant conformity assessment procedure. In addition, details about conformity assessment procedure and manufacture of the device should be included.

5.6 Medical Devices with Predetermined Classifications

Group A

These devices provide a secondary effect to the patient along with its main intended purpose. These devices also contain nonviable animal origin material, any materials of microbial or recombinant origin like hyaluronic acid. Some examples of such devices include wound dressings with collagen and heart valves with animal tissue leaflets.

Group B

This group includes breast implants; knee, hip, or shoulder joint replacement implants; contraceptive devices; active implantable medical devices; implantable accessories; active implantable medical devices; and active devices that are meant to control, monitor, or influence the working of an active implantable medical device.

Group C

This group contains devices like blood bags (with anticoagulant); ancillary medical devices (used in joint replacement surgery); devices meant for disinfecting, cleaning, rinsing, or hydrating contact lenses; contraceptive medical devices; and those that are non-implantable or invasive for long-term usage.

Group D

Medical devices like non-active medical devices that record X-ray diagnostic images are part of this group.

Group E

This group contains devices that would be used to clean another medical device physically, devices for export, and devices that consist of nonviable animal origin material and are designed to come in contact with the skin and are nonsterile.

5.7 Comparable Overseas Regulators for Medical Device Applications

The TGA accepts certifications from overseas regulators like the European union, US FDA, Health Canada, Medical Device Single Audit Program (MDSAP) Auditing Organization, and the Ministry of Health, Labor and Welfare and Pharmaceutical and Medical Devices Agency of Japan. The manufacturer has to follow a guidance developed by the TGA to include in their abridgement application.

5.8 Varying Entries in the ARTG: Medical Devices and IVDs

The sponsor would request the TGA to vary the entry in the ARTG if any previous information in the ARTG has changed. The variation can be requested in situations like information in the ARTG is no longer valid, manufacturer details have changed, GMDN code (Global Medical Device Nomenclature System Code) of the device has been revised, the device has a new intended purpose now, variants are added to the device, the device identifier has changed, the UPI (unique product identifier) of the device has been amended, sponsor desired to vary the list of IVD devices in the ARTG entry, etc.

5.9 Changing the Sponsor of Therapeutic Goods

The ATG needs to be informed within 3 months of the sponsor change along with the transfer assignment. The sponsor needs to submit a notification form with all the details; the ARTG entries are updated within 10 working days, and the new certificate can be downloaded after 24 h.

5.10 Clinical Evidence Guidelines: Medical Devices

This section outlines the clinical evidence guidelines for the following devices: total and partial joint prostheses, cardiovascular devices to promote patency or functional flow, implantable pulse generators, heart valve prostheses, and supportive devices – meshes, patches, and tissue adhesives. The clinical evidence is required by the Australian government to ensure the safety and performance of the device. The clinical evidence needs to remain on the register as long as the device is on the ARTG list. It may be re-requested at any time. The clinical evidence should consist of documented literature where the device has been used for its intended purpose. The risk or safety profile of the device can then be demonstrated such that all the undesirable effects and hazards associated with the device have been reduced. The classification of the device would dictate the amount of clinical evidence to be supplied along. This clinical evidence would be updated and reviewed regularly as new information based on post-market surveillance activities and as product experience become available.

5.11 ARTG Search

The ARTG register can be lawfully supplied in Australia. The Consumer Medicines Information (CMI), Product Information (PI), and public summary documents can be obtained from the ARTG. The sponsors can request cancellation of their entries into the ARTG. The secretary has to authorize these cancellations. The cancellation provisions in the Act that can be requested by the sponsor are:

- Cancellation of listed or registered therapeutic goods: section 30(1)(c)
- Cancellation of biologicals: section 32GA(1)(d)
- Cancellation of medical devices: section 41GL(d)

5.12 Regulatory Affairs Consultants

These consultants offer services like advice and assistance with the regulatory requirements. Listed are some of the industry organizations that can provide assistance with the regulatory requirements:

- ACCORD Australasia
- ARCS Australia

These are the names of the companies and they appear as it is on their website:

- Association of Therapeutic Goods Consultants Inc.
- AusBiotech

- Australian Dental Industry Association
- Australian Self-Medication Industry Association
- Complementary Medicines Australia (CMA)
- Pathology Technology Australia
- Medical Technology Association of Australia (MTAA)

5.13 Adverse Event Reporting

The sponsors would report the adverse events or the near adverse events that occur in Australia to the TGA's Incident Reporting and Investigation Scheme (IRIS). The definition of adverse event is the same in TGA as discussed in previous chapters. However, a near adverse event is an incident associated with the device that might have caused death or a serious injury if not for a timely intervention.

Exemptions to Reporting
There are eight exemption rules that can prevent the reporting of an adverse event:

1. Deficiency of a new device found by the user prior to its use, for example, if a sterile single-use device packaging is labeled with caution "do not use if package is opened or damaged" and the package seals are found opened.
2. Adverse event caused solely by patient conditions; such a condition should be preexisting or happening within the patient at the time of device use, for example, if the patient dies after dialysis because he/she had an end-stage renal disease.
3. Service life of the medical device, for example, a pacemaker loses its sensing after reaching the end of life, the elective replacement indicator has set out in due time according to the device specification.
4. Protection against a fault functioned correctly; this means that the design of the device protected against a hazardous situation. For example, an infusion pump stopped due to malfunction, and the alarm went on as intended and therefore, prevented any injury to the patient.
5. Remote likelihood of occurrence of death or serious injury, for example, a software bug is identified in a pacemaker supplied to the market, and the likelihood of occurrence of a serious injury with a particular setting is remote. Also no patients have experienced any adverse health effects.
6. Expected and foreseeable side effects that are documented in the manufacturer's instructions for use or labeling; an expected side effect that has been clearly documented in the manufacturer's submitted documents need not be reported.
7. Adverse events described in an advisory notice; if an adverse event occurs after the manufacturer issues an advisory notice, it does not need reporting.
8. Reporting exemptions granted by the TGA; the sponsor may request the TGA to exempt common and well-documented events from reporting or change it to periodic reporting on a case-by-case basis.

5.14 Process of Reporting

The following information needs to be supplied to the TGA's IRIS system in regard to an adverse event:

- Source of information and the details of the reporter
- Device identification
- ARTG number of the device
- Date of occurrence
- Elaborate description of the event
- Date of implant, if applicable
- Details of any investigations or corrective actions taken by the sponsor or manufacturer
- Information of any similar events

The report is submitted in three stages: initial report, follow-up report, and final report. The initial report would be prepared by the sponsors according to the legislative time frame, and additional information is given as it becomes available. The status of any additional investigations carried out by the manufacturer would be provided in the follow-up report. The final report would contain the things above and should be submitted within 90 days of the initial report.

5.15 Annual Charge Exemption Scheme

The Annual Charge Exemption (ACE) scheme gives a provision to exempt the annual charge for a good that is registered, listed, or included in the ARTG until it first starts generating turnover. The purpose of the scheme is to acknowledge the fact that TGA's post-market monitoring costs should only be acquired by goods that have been established into the market. This scheme allows sponsors to register their goods into the ARTG in advance before their marketing without annual charge. Once an ARTG entry begins generating turnover in Australia, the exemption ends, and the sponsor has to pay the annual charge for the respective ARTG entry each financial year till it is cancelled from the ARTG.

6 Japan Medical Device Regulations

The Pharmaceutical and Medical Device Agency (PMDA) and Ministry of Health, Labor, and Welfare (MHLW) regulate the medical devices and pharmaceuticals. They use a similar "risk-based classification system" to categorize medical device into four classes: class I being the lowest potential risk and class IV with the highest potential risk. In 2014, the Japanese Pharmaceutical Affairs Law (JPAL) was

replaced with Pharmaceutical and Medical Device Act (PMDA). The PMD covers major areas of device regulations like quality management system compliance, device registration, medical software, and third-party certifications. The manufacturers have to comply with the current PMD Act to market medical devices in Japan. There are three essential aspects to Japan's regulatory information:

(a) Classification and Product Registration

The PMDA follows the Japan Medical Device Nomenclature (JMDN) system, which is similar to US FDA's product code classification, where codes are fixed with reference to Global Medical Device Nomenclature (GMDN). These "generic names" are then classified from class I to IV depending on the potential risk associated with them. Class I devices contain the lowest potential risk as far as the patient health is concerned. Class I devices are registered through a process called "notification." All notification applications would contain a detailed device description (measurements, materials involved, etc.). Some examples include X-ray films, scalpels, and in vitro diagnostic devices. Class II devices include moderately low-risk medical devices, like digestive catheter, electronic endoscopes, and dental alloys. Class II devices have to undergo "certification" that is reviewed by a Registered Certification Body (RCB). These devices may be classified as either controlled medical device (approved by PMDA) or designated controlled medical device (certified by RCB). Those devices, which cannot be certified as class II devices would have to submitted for approval as class III and class IV devices. Class III medical devices present a relatively high risk to patients if they malfunction. Such devices include dialyzers, hemodialysis equipment, mechanical ventilation apparatuses, etc. Class IV devices are the highest-risk devices that may be life-threatening under a malfunction, for example, artificial cardiac valves, pacemakers, and stent grafts. Class III and class IV medical devices are specially controlled medical devices, class III medical devices can be reviewed by either RCB or PMDA, and class IV medical devices must be reviewed by PMDA only. CE mark and FDA approval are not accepted in Japan but can definitely speed up the registration process. The device registration does not expire in Japan; however, it needs to be renewed in every 5 years. All documents submitted to the PMDA or RCB have to be translated to Japanese.

(b) Foreign Manufacturer Registration (FMR)

The foreign manufacturers have to undergo FMR in addition to product registration to market their devices in Japan. A FMR certificate is valid for 5 years and should be renewed at least 5 months before the certification expires. The Designated Marketing Authorization Holder (D-MAH) or the Marketing Authorization Holder (MAH) would first obtain a business number by submitting a business number registration form. The Japanese regulatory officials from the PMDA would then perform audits/documentary inspection. After this the D-MAH or MAH would submit the FMR application.

(c) Device Reimbursement

After the regulatory approval of a medical device, it is mandatory to submit a reimbursement request to the MHWL already defined. There are six general reimbursement categories: A1, A2, B, C1, C2, and F. A and B categories contain already categorized medical devices, and C and F categories have relatively new devices. The decision on A and B devices is issued quickly, whereas for C devices, the applicant has to wait a little longer.

7 Singapore Medical Device Regulations

The Singapore regulation is called the Singapore Health Products Act of 2007, and it demands all medical devices to be certified by an accredited Certification Assessment Body (CAB) that is registered in the Singapore Medical Device Information and Communication System (MEDICS). All devices used for treatment in hospitals and patient clinics have to be certified and distributed under an "establishment license." This regulation prohibits the usage of any device by the hospitals and clinics that are not certified, registered, or legally distributed. This ensures the quality and integrity of all medical devices throughout the distribution process.

Some high-risk medical devices may qualify for an "abridged" product evaluation if they have already been approved by one of the following regulatory bodies: US FDA, EU Notified Body, Health Canada, Australia's TGA, and Japan's MHLW. The device submitted for abridges approval must be identical to that approved by the abovementioned authorities. In addition to certification by the Health Sciences Authority (HSA), registration and licensed distribution requirements and the supply and use of medical devices in Singapore may be subject to other regulations, such as the provisions of the Private Hospitals and Medical Clinics Act and the Radiation Protection Act. Requirements may differ with respect to the type of medical device under consideration. The manufacturers also have to maintain a quality management system that meets the requirements of HAS's already defined Good Distribution Practice for Medical Devices (GDPMDS) standard, which is similar to the international standard ISO 13485.

8 United Kingdom Medical Device Regulations

Medicines and Healthcare products Regulatory Agency (MHRA) is the authority which enforces the law on medical devices in the United Kingdom. The following regulations are important for supplying medical devices in the United Kingdom or Europe:

- The Medical Devices Regulations 2002 (SI 2002 No 618, as amended)
- The General Product Safety Regulations 2005 (SI 2005 No 1803)

These regulations fall under the Customer Protection Act from 1987 but are still used by MHRA today.

8.1 The Customer Protection Act from 1987

The MHRA can release prohibition notices to stop the supply of any goods which would be deemed unsafe or noncompliant with the regulations. They can warn the manufacture to issue warnings about devices that are unsafe. They can pass suspension notices for any device based on suspicion that safety provisions have been disobeyed. They can even forfeit orders for goods for the same reason. The MHRA can request additional information to contemplate their decision for a revoke or prohibition or to issue a warning.

8.2 The Medical Devices Regulations 2002

In this act, the MHRA can issue a compliance notice to the offenders and request the correction of noncompliance or a restriction notice to restrict the sale of a particular device or devices of a specific class or description.

8.3 The General Product Safety Regulations 2005

The manufacturer is responsible for ensuring that all the medical devices made, imported, distributed, or sold in the United Kingdom are safe for the consumers and follow the regulations set forth in regard to labeling. The GPSR requires all products to be safe in their regular and reasonable usage; therefore, all manufacturers have to demonstrate compliance with the safety regulations. To ensure this, they can take corrective action, recalls, and report safety incidents. They are also liable for their products under the Consumer Protection Act 1987 if their product causes harm or death to any of their consumers.

8.4 Failure to Comply with the Regulations

If MHRA feels that the manufacturer has committed a serious offence by not complying with these regulations or not meeting the conditions of a notice issued to them, then they may be subject to prosecution, which includes a penalty of an unlimited fine and/or imprisonment for 6 months.

8.5 Inspections

The MHRA can perform inspections of the manufacturing site at any time if they feel the need to do so. It follows the protocol in Consumer Rights Act 2015 that the MHRA can enter premises and can inspect the devices, can evaluate the manufacturing procedures and testing facilities, and can ask for business documents and detain any if required. Any information gathered in the course of an inspection will be considered confidential according to the confidentiality provisions in Article 20 of the Medical Devices Directive (93/42/EEC), article 19 of the In Vitro Diagnostic Medical Devices Directive (98/79/EEC), and article 15 of the Active Implantable Medical Devices Directive (90/385/EEC). These were included into UK legislation by the Enterprise Act 2002, which allows the release of information to third parties in certain circumstances.

8.6 Appeals Procedure

The manufacturer has the right to appeal any decision made by the MHRA through Chartered Institute of Arbitrators (CIArb). The appeal procedure would depend on the regulatory decision of the MHRA like prohibition notice (Consumer Protection Act, schedule 2, part 1), notice to warn (Consumer Protection Act, schedule 2, part 2), recall notice (General Product Safety Regulations, Regulations 15 and 17), clinical investigation notifications (Medical devices Regulations, Regulations 16 and 29), notified body designations (Medical Devices Regulations, Regulation 45), and applications for exceptional use of noncomplying devices (medical devices regulations, regulations 12, 26, and 39). Appeals against other regulatory decisions would be processed separately probably through courts. MHRA would notify the manufacturer of their regulatory decision along with their rights to appeal.

8.7 Exceptional Use of Noncomplying Devices

A manufacturer may request to supply a medical device that is noncompliant with the law if there are no options available. This is known as an "exceptional use of a non-CE marked medical device." There are separate guidelines for such devices under Regulation 12(5) of the Medical Devices Regulations 2002. This also includes active implantable medical devices in regulation 26 and for in vitro diagnostic medical devices under regulation 39(2).

8.8 Complaints

Complaints can be made about the behavior of MHRA personnel or advice given by them (except enforcement decisions) according to complaints procedure. All MHRA compliance inspectors and investigators are obligated to conduct their inspections and investigations according to internal operating procedures.

9 European Medical Device Regulations

The European regulation comprises of rules concerned with marketing, both placing and supplying, its human use, and accessories required for such devices. These regulations are also true for any clinical investigations that are being carried out for these devices (not discussed here). Medical devices with both medical and non-medical purpose have to satisfy all the requirements associated with devices with and without the intended purpose. The regulation does not apply to in vitro medical diagnostic devices, medicinal products, human fluids, cosmetic products, transplants, and products containing live biological organisms like bacteria and virus and food mentioned in the regulation. In this chapter, only the general requirements associated with the safety and performance of the device are discussed.

9.1 General Requirements

The medical device has to deliver the performance as intended by the manufacturer and would be designed and manufactured for the same. It should be safe and effective while doing so and should not affect the clinical condition or safety of the patient or users in general. The manufacturers will supply the safety documentation along with the device, which would include not only the risk management plan but also any predicted hazards and estimated risks. The manufacturer shall employ risk control measures during the design and manufacture of the device. The manufacturer would also manage risks so that the residual risk associated with each hazard is limited to the acceptable level. For this, the manufacturer would erase or decrease the risks through safe design and manufacture. He would also take appropriate protection measures like alarms and provide safety information and user manual. In case of user error-related risks, the manufacturer shall reduce the risks related to the ergonomic features of the device and the usage environment and provide training for use wherever possible. The packaging of the device would be designed to prevent it from damage during transport and storage.

9.2 Requirements Regarding Design and Manufacture

The materials used to design the device would be chosen in regard to (a) toxicity, (b) compatibility between materials and substances and biological tissues and body fluids, (c) compatibility between different parts of the device, (d) impact of processes on material properties, (e) mechanical properties of used materials, (f) surface properties, and (g) confirmation that the device meets the defined chemical and/or physical specifications. The device would be designed and manufactured to reduce the risk imposed by substances or particles like water, degradation products, and residues. The device or part of device that will come in contact with the body directly or through body fluids will contain only 0.1 %w/w of the respective substance. This information would also be present on the label of the device. The device packaging has to be sterilized by approved methods. In case of non-sterilized devices, the cleanliness of the product has to be maintained while packed and should be sterilized before use according to manufacturer's instructions. The labeling should be clear in terms of sterile and nonsterile devices. The devices shall be designed to prevent infection and microbial contamination to patients in instances like cuts and pricks. The design of the device shall allow easy and safe handling, reduce any possible microbial leakage from the device, and prevent device contamination from any human fluids. The packaging and labeling of the devices would reflect the same. The devices that contain tissues or cells of animal origin or their nonviable derivatives would have to be subjected to appropriate veterinary controls: sourcing, processing, preservation, testing, and handling of tissues, cells, and substances of animal origin; safety in terms of viruses and other transmissible agents would be ensured by appropriate validation methods for elimination of such agents during manufacturing while maintaining the clinical benefit of the device. In order to reduce the risk imposed by medical devices that are used by laypersons, the instruction for use provided by the manufacturer should be very simple and easy to understand. Its design should ensure safety at each stage of use or after training, reduce the risk associated with usage like cuts and pricks, and finally reduce error by the user during handling.

9.3 Requirements Regarding the Information Supplied with the Device

In previous chapters and other countries' regulations, labeling has been covered in detail. The European regulation entails similar instructions regarding labeling. In brief, each device has to have a label that contains its identity, manufacturer's name, and safety and performance profile. The label would appear on the device or its packaging or both. It would contain the name of device, manufacturer's trademark, address of the manufacturer, contents of the device (biological or not), lot number/serial number, indication of clinical or nonclinical use, and in case of implants the

serial number. The device shall contain instructions of use that are easily understood by the user or the website link where they can be found. The information on the label should be relevant to the respective device and must contain a radio-frequency identification (RFID) or bar codes. The risk information like device limitations, contraindications, precautions, or warnings has to be supplied with the device. The manufacturer has to use internationally recognized symbols in the supplied information wherever possible. In places where this is not possible, the manufacturer has to define those symbols in the accompanying documentation.

9.4 Post-market Surveillance

The manufacturer shall plan, establish, document, implement, maintain, and update a post-market surveillance system that is relevant to the risk class of the product and type of device. This post-market surveillance system would be employed to gather, record, and analyze relevant data on the quality, performance, and safety of a device for its entire lifespan and to decide, implement, and monitor any preventive and corrective actions that need to be taken. Some examples are updating of benefit-risk determination and improving risk management, updating clinical evaluation, updating the summary of safety and clinical performance, etc. If during the post-market surveillance a need for preventive or corrective action arises, the manufacturer shall take appropriate measures and inform the respective authorities or notified body.

9.5 Cooperation Between Member States, Medical Device Coordination Group, Expert Laboratories, Expert Panels, and Device Registers

The Member States shall allocate the competent authority or authorities that would be responsible for the implementation of this regulation. These authorities would have the powers, resources, equipment, and knowledge necessary to carry out the tasks associated with this regulation. The names and contact of the competent authorities shall be given to the Commission which would then publish a list. The authorities shall cooperate with each other and the Commission. A medical device coordination group (MDCG) would be appointed by each member state for 3 years that can be renewed. The members of MDCG would be chosen based on their expertise and competence in medical device field and in vitro diagnostic medical devices. The MDCG would (a) establish rules for the acceptance of opinions or recommendations regarding cases of urgency, (b) assign tasks to reporting and co-reporting members, and (c) implement the regulation regarding the conflict of interests and (d) functioning of subgroups.

9.6 Confidentiality, Data Protection, Funding, and Penalties

The confidentiality of information shall be maintained which would include any personal data or commercially confidential data for the purpose of inspections, investigations, or audits. The Commission shall cover any costs associated with joint assessment activities. The penalties shall be imposed in case of infringement of the provisions of this regulation, and necessary measures would be taken for their implementation.

References

1. @TUVSUD. "UNDERSTANDING THE REGULATORY REQUIREMENTS FOR MEDICAL DEVICES IN INDIA", https://www.tuvsud.com/en/industries/healthcare-and-medical-devices/medical-devices-and-ivd/medical-device-market-approval-and-certification/regulation-of-medical-devices-in-india
2. @Regdesk. "An Overview of Medical Device Regulations in China", January 9, 2019, https://www.regdesk.co/an-overview-of-medical-device-regulations-in-china/
3. Medical Devices Regulations (SOR/98-282)
4. Medicines Act 1981
5. Therapeutic Goods (Medical Devices) Regulations 2002, Statutory Rules No. 236, 2002, made under the, Therapeutic Goods Act 1989
6. @TGA. "Australian regulatory guidelines for medical devices (ARGMD)". October 18, 2019, https://www.tga.gov.au/node/5308
7. @Regdesk. "An Overview of Medical Device Regulations in Japan", January 20, 2019, https://www.regdesk.co/an-overview-of-medical-device-regulations-in-japan/
8. @GOV.UK, "Medical devices: the regulations and how we enforce them", February 26. 2019, https://www.gov.uk/government/publications/report-a-non-compliant-medical-device-enforcement-process/how-mhra-ensures-the-safety-and-quality-of-medical-devices
9. @EUR-Lex, "REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL", April 5, 2017, https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0745-20170505#tocId142

Index

P. S. Timiri Shanmugam et al. (eds.), *Medical Device Guidelines and Regulations Handbook*, https://doi.org/10.1007/978-3-030-91855-2