Chapter 4
Definition and International Regulations for Medical Devices

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Abstract The term medical device refers to a wide variety of products. They range from simple low-risk devices such as stethoscopes and syringes, through imaging device and in vitro diagnostic, up to high-risk biocompatible implants, such as orthopaedic prostheses and pacemakers.

The number and variety of medical devices are increasing as new software and hardware applications, new materials and new combination products are developed and to classify these according to the intended purpose and the different options may be a difficult task.

The identification of a product as a medical device and the further classification into classes of risk is the base for the application of the correct regulatory path worldwide, although differences exist at national level in such classifications.

The development of consistent, harmonized definitions for the terms "medical device" and "in vitro diagnostic medical device" would offer significant benefits to the manufacturer, user, patient and to regulatory authorities. This can also support the global convergence of regulatory systems.

This chapter aims to give a comprehensive description of the different regulations concerning the medical devices worldwide with special reference to the EU Medical Device Directive. The role and importance of the technical standards are also described.

Introduction

More than 20,000 types of medical devices now exist. They range from simple low-risk devices such as stethoscopes and syringes, through imaging device and in vitro diagnostic, up to high-risk biocompatible implants, such as orthopaedic prostheses and pacemakers.

The number and variety of medical devices are increasing as new software and hardware applications, new materials and new combination products are developed

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The development of consistent, harmonized definitions for the terms "medical device" and "in vitro diagnostic medical device" would offer significant benefits to the manufacturer, user, patient or consumer, and to regulatory authorities and support global convergence of regulatory systems.

An attempt to develop a consistent, harmonized definition for the terms "medical device", and an "in vitro diagnostic medical device", has been carried out by The Global Harmonization Task Force of the World Health Organization.

The goals of the Global Harmonization Task Force (GHTF) go beyond proposing definitions, since also include standardizing of nomenclature for defining and naming innovative technologies, classifying the devices for regulatory approval (registration) and encouraging convergence in the evolution of regulatory systems for medical devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by those regulatory means considered the most suitable. The final goal is to have an international classification, coding and nomenclature for medical devices that would be accepted and used worldwide.

4.1 The Medical Device Concept and Classification

The term "medical device" covers a very wide range of products, such as instruments, software and materials (i.e. substances). Although the definitions of medical device may differ among national legislations, most of the definitions are based upon two principles:

1. The medical purpose: A medical device is intended to be used to diagnosis, prevention, monitoring, treatment or alleviation of a disease or injury,
2. The mechanism of action: The principal mechanism of action of a medical device should not be based on pharmacological, immunological or metabolic mechanisms.

The medical purpose differentiates medical devices from everyday devices, whereas the mechanism of action differentiates medical devices from pharmaceutical products.

The adoption of these two principles is reflected in the definitions proposed in 2012 by the Global Harmonization Task Force:

> *A medical device is an article, instrument, apparatus or machine (including mobile medical applications and software) that is intended by manufacturer to be used alone or in combination in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some*

health purpose. Typically, the purpose of a medical device is not achieved by pharmacological, immunological or metabolic means.

A subset of medical devices, defined as devices which, whether used alone or in combination, are intended by the manufacturer for the examination in vitro of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. They include reagents, calibrators, control material and test kits. [1]

The classification of medical devices is a "risk-based" system based on the vulnerability of the human body taking account of the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways in order to determine classification, e.g. duration of contact with the body, degree of invasiveness and local vs. systemic effect. These criteria, also referred to as "classification rules" have been object of a proposal from the Global Harmonization Task Force (GHTF) [2]. The proposal of the GHTF introduces a device classification system consisting of four classes where Class A represents the lowest hazard and Class D the highest.

Although these proposals have not yet been formally adopted at national levels, the definitions and classification rules found in the regulatory frameworks of the major markets (i.e. Europe, United States and Japan) are consistent with the definitions and classification rules laid down by the Global Harmonization Task Force.

4.1.1 Definition of Medical Device in Europe

For the European Market, the definition of medical device was originally given in Article 2 of the Council Directives 90/385/EEC [3], 93/42/EEC on medical devices (Medical Device Directive—MDD) [4], and then amended in the Directive 2007/47/EEC (mostly to include stand-alone software products) [5]. The new released Regulation 2017/745 on Medical Device (Medical Device Regulation—MDR) [6] has further modified the definition to include the "in vitro" diagnostic medical device:

"Medical device" means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal 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.*

The following products shall also be deemed to be medical devices:

- *devices for the control or support of conception;*
- *products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*

Thus, as mentioned above, a product will be considered to fall within the definition of a medical device if it has a medical purpose and if the product functions primarily in a way that is not metabolic, immunological or pharmacological. The determination of whether a product is considered to have a medical purpose will be based on the intended purpose declared by the manufacturer.

The cases where it is not clear whether a product is a medical device, fall within the competence of the Competent Authorities of the Member States where the product is on the market. However, to help in the decision, the European Commission has published and keeps updated a Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices [7].

Once a product meets the criteria to be considered a medical device, a further distinction between medical device and "in vitro" medical device has to be made. This distinction has an impact on the regulatory path to be followed for put the product into the European Union (EU) market.

For a medical device, a further distinction between "Active Implantable Medical Device" and "Medical Device" has to be made. Finally, for (not-Active Implantable) medical device a class of risk (I, Is, Im, IIa, IIb or III) has to be assigned. Classification rules were laid down in Annex IX of MDD and are now laid down in Annex VIII of MDR. The document "MEDDEV 2. 4/1-classification of medical devices" provides a practical guide and examples to rule interpretation and application [8]. A more detailed examination of the risk classes will be given in the following paragraphs dedicated to regulations and directives.

4.1.2 Definition of Medical Device in the United States

For the US market, the definition of a medical device is given in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act [9]. A device is:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. *recognized in the official National Formulary, or the United States Pharmacopoeia (USP), or any supplement to them,*
2. *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
3. *intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).*

If a product is labelled, promoted or used in a manner that meets the above definition, it will be regulated by the Food and Drug Administration (FDA) as a

medical device and is subject to premarketing and post-marketing regulatory controls, according to its class of risk (I, II or III).

In cases where it is not clear whether a product is a medical device, the Center for Device and Radiological Health (CDRH) of FDA has established and maintains a public classification database [10] which contains products FDA considers devices and the associated codes developed to support its regulatory and administrative processes. In addition, if the preceding information does not result in determining whether a product is a device, the Centre's Device Determination Officers, Office of Compliance, may be contacted.

4.1.3 Definition of Medical Device in Japan

For the Japanese market, the definition of medical device was originally laid down in the Japan's Pharmaceutical Affairs Law (PAL). The intent of PAL was to harmonize requirements by incorporating the guidance documents of the Global Harmonization Task Force (GHTF). This includes quality management systems (QMS) requirements based on the ISO 13485 norm.

Article 2, Paragraph 4, of the Pharmaceutical Affairs Law defines medical devices as "*instruments and apparatus intended for use in diagnosis, cure or prevention of diseases in humans or other animals; intended to affect the structure or functions of the body of man or other animals*" [11].

Pharmaceutical Affairs Law (PAL) was replaced in 2014 by the Pharmaceuticals and Medical Devices Act (PMD Act), also known as the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The definition of medical device was not changed, but in the text is further specified that the term "medical device" refers to: *any instruments, machines, apparatus, materials, software, reagent for in vitro use, and other similar or related articles, which is used in diagnosing, curing, alleviating, or directly preventing human diseases, regulating fertility, or which may affect the body structure or functions of human beings, and do not achieve its primary intended function by pharmacological, immunological or metabolic means in or on the human body* [12].

Under Japan PMDA regulations, a medical device can be classified, as a General Medical Device (Class I), Controlled Medical Device (Class II) or a Specially Controlled Device (Class III and Class IV), depending on the risk level.

4.2 Regulations (EU, USA, Japan)

Despite global efforts to harmonize regulation of medical devices via groups such as the Global Harmonization Task Force (GHTF), and the International Medical Device Regulators Forum there is a huge discrepancy among regulatory requirements all over the world.

The differences lie not only in the classification of devices, but also in the overall process, the quickness of approvals, their applicability across regions and the expense involved, although it is acknowledged worldwide that a global approach to auditing and monitoring the manufacturing of medical devices could improve their safety and oversight on an international scale.

The three main regulatory frameworks are: the CE-Mark, the US-FDA approval, and the Japanese PMDA. Each of them differs in the aim of the regulation and in the process involved. CE-marking was established mainly to guaranty the safety of the device, as a requisite for the free commercialization in all the EU Countries. The US FDA also focuses on safety but with the additional requirement of evaluating the efficacy. Japanese PMDA looks to quality, efficacy and safety.

4.2.1 European Regulatory Framework: CE-Mark

Medical devices, as many other products, require CE-marking before they can be sold in the European Economic Area (EEA). CE-marking proves that the device has been assessed and meets EU safety, health and environmental protection requirements. It is valid for devices manufactured both inside and outside the EEA, that are then marketed inside the EEA.

The EU-wide requirements are laid down in directives or regulations that cover different products or product sectors. For medical devices, the relevant directives were adopted more than 25 years ago and represented a significant change for manufacturers and competent authorities:

- Directive 90/385/EEC regarding active implantable medical devices (AIMDD)
- Directive 93/42/EEC regarding medical devices (MDD)
- Directive 98/79/EC regarding in vitro diagnostic medical devices (IVDD)

Based on the data collected, and on the experience gained during these years of application, the Directives were amended in 2010 (Directive 2007/47/EC).

In 2017, the Directives have been superseded by the adoption of the Regulation (EU) 2017/745 on Medical Devices (MDR) and Regulation (EU) 2017/746 on In Vitro Diagnostic Devices Regulation (IVDR). A “Regulation” (unlike a Directive) is directly applicable as a law and has consistent effect in all EU Member States.

The EU's Medical Device Regulation (MDR) was officially published on 5 May 2017 and came into force on 25 May 2017. The MDR will replace the EU's current Medical Device Directive (93/42/EEC) and the EU's Directive on active implantable medical devices (90/385/EEC).

From 26 May 2020, new devices will have to meet the requirements of the MDR in order to be placed in the European market.

Devices holding a certificate from a European Notified Body under either the Medical Device Directive (93/42/EEC) or the Active Implantable Medical Devices Directive (90/385/EEC) have an additional grace period and may continue to be placed on the market until 26 May 2024 if the manufacturer fulfil the specific prerequisite requirements drawn in the MDR.

Due to the COVID-19 outbreak, the application of MDR have been postponed by a year in a bid to prevent shortages in getting key equipment on the market during the coronavirus pandemic. The Medical Devices Regulation (MDR) was due to be enforceable on 26 May 2020 but will now take effect on 26 May 2021.

Fig. 4.1 Calendar for the introduction of the MDR application

The MDR provides for a transition period of 3 years and fully applies on 26 May 2020.[1] The IVDR provides for a transition period of 5 years and will fully apply from 26 May 2022. During the transition period, manufacturers can place devices on the market under the currently applicable EU Directives (93/42/EEC, 98/79/EC and 90/385/EEC) or under the new Regulation. Due to the COVID-19 pandemic, an amendment to the MDR was adopted on 24 April 2020 by European Commission, which postponed the application of most of its provisions by 1 year, until 26 May 2021. The European Commission considered such a delay necessary given that the public health crisis has created a demand for substantial additional resources and medical devices of vital importance, such as medical gloves, surgical masks, equipment for intensive care and other medical equipment, which could not have been reasonably anticipated at the time of adoption of the MDR (see summary in Fig. 4.1).

For medical devices and active implantable medical devices, the technical requirements are detailed in Annex I of each of the MDD and AIMDD. These requirements are called Essential Requirements (ER). There are 13 ERs in the MDD and 16 in the AIMDD. The General Safety and Performance Requirements (SPRs) listed in Annex I of MDR have replaced the Essential Requirements. The scope and topics are consistent overall with the ERs of the Directives. However, there are a few notable differences.

For some medical devices, other regulations may be also applicable: the Restriction of Hazardous Substances (RoHS) Directive, the General Data Protection Regulation (GDPR) or the Machinery Directive since those requirements are more specific than the essential requirements set out in Annex I to the MD or AIMD

[1] Status May 2021: the full application of MDR has been postponed for organizational reasons.

Directives or MDR. In other cases (e.g. Low Voltage Directive and Electromagnetic Compatibility Directive) since the prescriptions of the Medical Device Directives/Regulation are more restrictive, there is no requirement to demonstrate the compliance with these Directives.

It is up to the manufacturer to make sure that the product meets all the EU legal requirements. Unless the device is a low-risk device, special conformity assessment bodies ("Notified Bodies") must verify that the specific technical requirements are met. The conformity assessment usually involves an audit of the manufacturer's quality system and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device.

Thus, in order to choose the proper certification path, the medical device shall be **classified** according to the class of risk laid down in the respective Directive/Regulation.

4.2.2 CE-Mark Device Classification

According to the European framework, there are four classes of medical devices: Class I, IIa, IIb and III. The medical devices of Class III hold the highest risk.

The classification rules are laid down in Annex IX of the MDD Directive (Annex VIII of the MDR). A guideline to classification can be found in document MEDDEV 2.4/1 [8].

- **Class I** Medical Devices: Medical devices class I have the lowest perceived risk. Several non-invasive, non-active devices belong to this class (e.g. plasters, scalpels, otoscopes, wheelchairs. . .). This class has also two subclasses: "**Is**" if the medical device is sterile, e.g. a personal protection kit; "**Im**" if the medical device has measuring functions, e.g. stethoscope.
- **Class IIa** Medical Devices: This class includes several active diagnostic and therapeutic devices such as hearing aids, diagnostic ultrasound machines, ECG and EEG devices, etc. They usually constitute low- to medium-risk. Patients should use them for a short-term period, any less than 30 days.
- **Class IIb** Medical Devices: It include medical devices such as long-term corrective contact lenses, surgical lasers, defibrillators and others. They are medium- to high-risk devices, and patients may use them for a period longer than 30 days.
- **Class III** Medical Devices: In that class, all medical devices have the highest risk possible. Such devices are, for instance, cardiovascular catheters, aneurysm clips, hip-joint implants, prosthetic heart valves and others.

No classes of risk are defined for active implantable devices (e.g. pacemakers, implantable cardioverter defibrillators, cochlear implants implantable nerve stimulators), since these devices are regulated by their own directive (AIMD). In the MDR, AIMD related devices will be classified as Class III.

In the near future, due to the stricter rules of the new Regulation (MDR), the class of some devices may change (e.g. up-classification of some stand-alone software products, up-classification of external defibrillators).

4.2.3 Major Changes Introduced by the MDR

Even if MDR is not radically different from MDD, additional work will be required to companies who want to continue supplying their devices beyond 2020. Most of the new requirements are extensions to already existing requirements. The current four classes I, IIa, IIb and III are retained without change, and the classification rules are mostly the same, with some changes related to substances, up-classification of software and of some specific devices. The essential requirements are still listed in Annex 1 of the MDR, are now renamed as "general requirements" and have been extended. All medical devices that incorporate electronic programmable systems and software or that are medical devices in themselves shall be developed and manufactured in accordance with the state of the art taking into account the principles of risk management, including information security, as well as to set out minimum requirements concerning IT security measures, including protection against unauthorized access.

The manufacturers may choose among different certification routes, but with fewer options than before.

The requirements related to post-market surveillance (PMS) have been expanded. The MDR defines post-market surveillance as a proactive and systematic process which manufacturers implement and carry out (with other economic operators) in order to take corrective and preventive action (CAPA) in accordance with information on medical devices and their performance. Companies have to institute and keep up to date a systematic procedure to collect and review experience gained from devices they place on the market and produce a PMS Report or, depending on the device class, a Periodic Safety Update Report (PSUR). The aim of the post-market surveillance system is to actively and systematically gather, record and analyse relevant data on the quality, performance and safety of a device throughout its entire lifetime. This allows manufacturers to continuously update the risk-benefit assessment and to initiate necessary measures without delay. Manufacturers are obliged to collect and assess all information about their medical devices and related devices from competitors.

MDR requires manufacturers to prepare and implement a post-market surveillance plan (Article 84), which is part of the technical documentation and proves compliance with the PMS requirements of the MDR. Annex III specifies the requirements and the content of such a post-market surveillance plan, and covers at least:

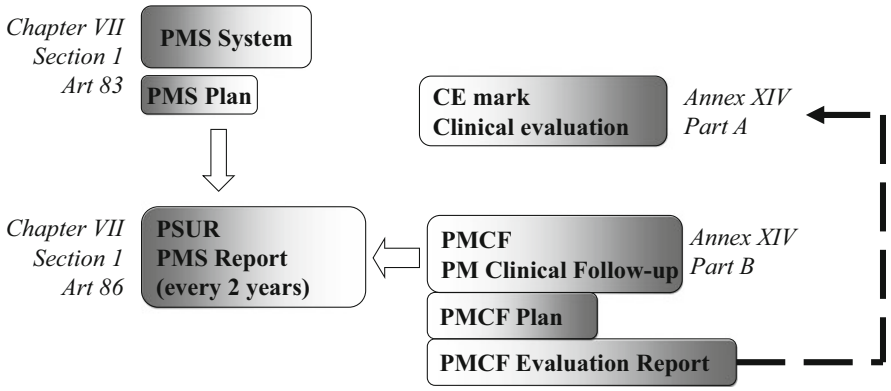

Fig. 4.2 Relation among the Post-Market Clinical Follow-up (PMCF), the post-market surveillance (PMS) plan and Periodic Safety Update Report (PSUR)

- *a proactive and systematic process to collect any information referred to in point (a). The process shall allow a correct characterization of the performance of the devices and shall also allow a comparison to be made between the device and similar products available on the market.*
- *effective and appropriate methods and processes to assess the collected data.*
- *suitable indicators and threshold values that shall be used in the continuous reassessment of the benefit-risk analysis and of the risk management as referred to in Section 3 of Annex I.*
- *effective and appropriate methods and tools to investigate complaints and analyse market-related experience collected in the field.*
- *methods and protocols to manage the events subject to the trend report as provided for in Article 88, including the methods and protocols to be used to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period.*
- *methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and user.*
- *reference to procedures to fulfil the manufacturers obligations laid down in Articles 83, 84 and 86.*
- *systematic procedures to identify and initiate appropriate measures including corrective actions.*
- *effective tools to trace and identify devices for which corrective actions might be necessary.*
- *a Post-Market Clinical Follow-up (PMCF) plan as referred to in Part B of Annex XIV, or a justification as to why a PMCF is not applicable.*

The relation among the PMCF, the PMS plan and PSUR is depicted in Fig. 4.2. MDR has introduced the Unique Device Identification (UDI). 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. Although UDI is a new requirement in Europe, it has been an established requirement in the United States.

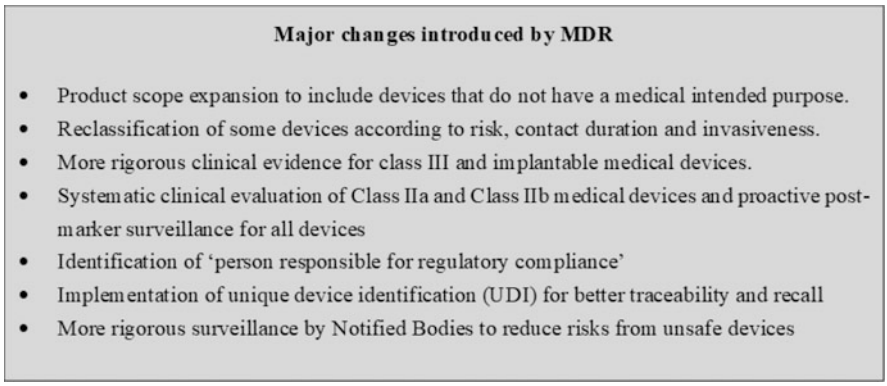

Fig. 4.3 Major changes introduced by the MDR

There are two requirements in the MDR which are novel (see also Fig. 4.3):

- Company shall appoint at least one person responsible for ensuring the regulatory compliance (the requisite expertise this person should have are laid down in Article 15).
- The extension of the scope of the medical device regulations to products without an intended medical purpose but which are analogous to devices with a medical purpose. This is aimed at medical device like products typically intended for cosmetic purposes (e.g. coloured non-corrective contact lenses). Annex XVI of MDR contains a list of groups of such products.

4.2.4 CE-Mark Certification and Declaration of Conformity

According to the European framework, if a medical device is in any other class apart from class I, a Notified Body assessment is required that the medical device fulfils the essential requirements of the respective CE directives.

For medical devices belonging to class IIa, IIb or III medical device, the declaration of compliance (CE Declaration) will have to be backed up with a Notified Body assessment (CE Certificate). Only then, the product can be placed on the market. The conformity assessment of the medical devices by the Notified Body may include an audit of the technical documentation and a quality system/product inspection, and to be focused on one or more aspects of the device design and production as summarized in Table 4.1.

The conformity assessment may follow different procedures, as listed in Annexes II, III, IV, V and VI of the MDD Directive. MDR has reduced the certification routes options, which are now listed in Annex IX to XI [6].

Table 4.1 Notified body assessment for CE certificate

Device class	Notified body (CE certificate)	Note
Class I	Not required	Manufacturer self-declaration
Class Is, Im	Required	Assessment by the Notified Body limited to measurement and sterilization issues
Class IIa	Required	Assessment of design/project by Notified Body not required Assessment of specific procedures of the Quality Management System by the Notified Body
Class IIb	Required	Assessment of Technical Documentation and of Quality Management System by the Notified Body
Class III and active implantable devices	Required	Assessment of Technical Documentation and Quality Management System by the Notified Body

4.3 US Regulatory Framework: FDA Notification and Approval

Medical devices marketed in the United States are subject to the regulatory controls in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the regulations in Title 21—Code of Federal Regulations [9].

The regulatory process with FDA is mainly based on the equivalence principle. The philosophy of this process involves proving substantial equivalence between the new device and the predicate (legally marketed) device, rather than an independent demonstration of the new device safety and effectiveness. The substantial equivalence should be not only in terms of technological and design characteristics but also on performance data and should have same intended use as the predicate device. If substantial equivalence cannot be established, the device generally requires premarket approval (PMA).

The first step in preparing a device for marketing is to classify the device. A medical device is defined by law in the section 201(h) of the FD&C Act, and the classification, which may be found in the Code of Federal Regulations, determines the regulatory path and regulatory requirements for your device, i.e. the type of premarketing submission/application required for FDA clearance to market. The marketing pathways include Premarket Notification (510(k)), De Novo Classification Request, Exempt, Premarket Approval (PMA), Product Development Protocol (PDP), Humanitarian Use Exemption (HDE) and Biologics License Application (BLA).

4.3.1 FDA Device Classification

Device classification depends on the intended use of the device and upon indications for use. Indications for use can be found in the device's labelling but may also be

conveyed orally during sale of the product. A discussion of the meaning of intended use is contained in the 510(k) Programme: "Evaluating Substantial Equivalence in Premarket Notification" (510(k)). In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

The Food and Drug Administration (FDA) has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

4.3.2 FDA Premarket Approval and Premarket Notification Process

The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If your device is classified as Class I or II, and if it is not exempt, a 510k will be required for marketing. For Class III devices, a premarket approval application (PMA) will be required.

As indicated in Table 4.2, all classes of devices are subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II and III.

Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application.

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to an

Table 4.2 Regulatory controls required by FDA

Device class	Regulatory controls	Notification/ approval	Note
Class I	General controls	510k premarket notification	Unless exempted
Class II	General controls and special controls	510k premarket notification	Unless exempted
Class III	General controls and premarket approval	Premarket approval application (PMA)	Unless your device is a pre-amendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) In that case, a 510k will be the route to market

already legally marketed device that is not subject to PMA. The 510(k) notification should include a physical description of the new device, together with an explanation of its intended use, principles of operation, power source, composition, and other information necessary to understand the device.

4.4 Japanese PMDA

Japan's Ministry of Health, Labour and Welfare (MHLW) is the regulatory body that oversees food and drugs in Japan, which includes creating and implementing safety standards for medical devices and drugs. In conjunction with the MHLW, the Pharmaceutical and Medical Device Agency (PMDA) is an independent agency that is responsible for reviewing drug and medical device applications. The PMDA works with the MHLW to assess new product safety, develop comprehensive regulations and monitor post-market safety.

Medical devices are regulated by the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as "the Pharmaceuticals and Medical Devices Act"), which came into effect in November 2014.

Medical Devices are classified by risk base concept, into four classes. All devices shall be in conformity with the Essential Principles (Eps). Essential Principles are revised according to the GHTF document on Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices [13].

4.4.1 Japan Medical Device Classification

Under Japan PMDA regulations, a medical device can be classified as a General Medical Device (Class I), Controlled Medical Device (Class II) or a Specially Controlled Device (Class III and Class IV), depending on the risk level. A summary is given in Table 4.3.

For General Medical Devices, only a notification/self-declaration is required, and the product does not need to undergo the approval process by the MHLW and PMDA.

Controlled Medical Devices can be designated to be certified by an authorized third-party certification entity or reviewed by the Pharmaceutical and Medical Device Agency (PMDA).

Specially Controlled Medical Devices must be reviewed and approved by the PMDA and Ministry of Health, Labour and Welfare (MHLW).

Table 4.3 Classification and regulation regarding medical devices in Japan

GHTF classification	Category	Regulatory requirements		
Class A	Extremely low risk e.g. X-ray film	General MDs (Class I)	Self-declaration: approval of the product is not required, but marketing notification is necessary	
Class B	Low risk e.g. MRI, digestive catheters	Controlled MDs (Class II)	Third-party Certification: Certification by a registered certification body is required	Minister's Approval (Review by PMDA) The Minister's approval for the product is required
Class C	Medium risk e.g. dialyzer	Specially Controlled MDs (Class III & IV)		
Class D	High risk e.g. pacemaker		Minister's Approval (Review by PMDA) The Minister's approval for the product is required	

4.4.2 PMDA Process

The Japanese approval process is essentially the approval of two aspects:

- Device: This involves review against Essential Principles (EP) and Summary Technical Documentation (STED) data subsets. EPs are specified in "the Standards for medical devices" as stipulated by the Japanese law. EPs cover design and manufacture (toxicity, compatibility, hardness, wear and degree of fatigue, handling, etc.), risk management, performance and function, durability, transport and storage and benefits of device. The Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) is a practical method to harmonize device regulation and bring Japan in line with other international regulatory bodies. Similar in principle to FDA 510(k) it attempts to show equivalence of a new device with a predicate device. It attempts to develop a common regulatory format for all the major regulatory bodies.
- Manufacturing facilities: data reliability, GLP, GCP, GMP conformity, post-approval inspection.

Each device is reviewed depending on its specific risk:

1. For review of general medical devices, a self-declaration system is adopted.
2. Designated Controlled Medical Devices are to be certified by the third-party certification bodies based on Certification Criteria (discussed below) which are pre-authorized by the Minister of Health, Labour and Welfare (hereafter MHLW). Other Controlled Medical Devices are reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA).
3. Specially Controlled Medical Devices are to be reviewed by PMDA and approved by the MHLW. They are reviewed based on separately specified approval criteria or Guidance Documents, which are authorized by the MHLW.

Where some devices comply with specified certification criteria and authorized by the MHLW they are to be reviewed and certificated by the third-party certification bodies as designated specially controlled medical devices.

PMDA reviewing applications for medical devices are as follows:

1. New medical devices: marketing applications for medical devices that have a clearly different structure, usage, indication, performance, etc., as compared to those that have already been approved for marketing.
2. Improved medical devices (with clinical data): marketing applications for medical devices that do not fall under "new medical devices" or "generic medical devices".
3. Improved medical devices (without approval criteria, without clinical data): marketing applications for medical devices that do not fall under "new medical devices" or "generic medical devices" (limited to devices for which no clinical data are required to be submitted).
4. Generic medical devices (without approval criteria, without clinical data): marketing applications for medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. (limited to devices for which no clinical data are required to be submitted).
5. Generic medical devices (with approval criteria, without clinical data): marketing applications for medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. (limited to devices for which no clinical data are required to be submitted.) and that comply with approval criteria (discussed below).

4.5 International Technical Standards

Standards play a significant role in the design, production, post-production and regulation of medical devices throughout their lifecycle. International standards offer important technical tools for conformity assessment, helping the evaluation that devices are safe and perform as intended.

Standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand. Standards can be particularly valuable as they reflect the state of the art and "*. . . generally reflect the best experience of industry, researchers, consumers and regulators worldwide, and cover common needs in a variety of countries. . .*" [13].

In general, the use of standards is voluntary, except in those particular cases where certain standards have been deemed mandatory by a regulatory authority.

Standards are created and published by national or international standards organizations or by regulatory authorities. As for medical devices, the most relevant bodies are listed below:

International Standards Development Organizations:

- IEC—International Electrotechnical Commission
- ISO—International Organization for Standardization

European Standards Development Organizations:

- CENELEC (European Committee for Electrotechnical Standardization) (https://www.cenelec.eu)
- CEN (European Committee for Standardization) (https://www.cen.eu)

US Standards Development Organizations:

- AAMI Association for the Advancement of Medical Instrumentation (http://www.aami.org)
- ANSI American National Standards Institute (https://www.ansi.org/)
- ASTM American Society for Testing and Materials (https://www.astm.org)

Japanese Standards Development Organization:

- JISC Japanese Industrial Standards Committee (https://www.jisc.go.jp)

For some standards, the development may be done by joint commissions (e.g. IEC and ISO).

Various terms are used to describe the characteristics of a standard. These are not necessarily mutually exclusive:

- basic safety standards (also known as horizontal standards)—standards indicating fundamental concepts, principles and requirements with regard to general safety aspects applicable to all kinds or a wide range of products and/or processes (e.g. standards concerning risk assessment and control of medical devices).
- group safety standards (also known as semi-horizontal standards)—standards indicating aspects applicable to families of similar products and/or processes referring as far as possible to basic safety standards (e.g. standards concerning sterile or electrically powered medical devices).
- product safety standards (also known as vertical standards)—standards indicating necessary safety aspects of specific products and/or processes, referring, as far as possible, to basic safety standards and group safety standards (e.g. standards for infusion pumps or for anaesthetic machines).

Standards covering different aspects of particular matter (e.g. safety of electrical medical device) or different types of device within a particular group (e.g. active implantable device) may have complex hierarchical structures (e.g. precedence) and interrelations. Standardized rules are used for the naming of standards belonging to the same series ("family").

An example of structure and naming adopted in IEC family of standard is depicted in Fig. 4.4.

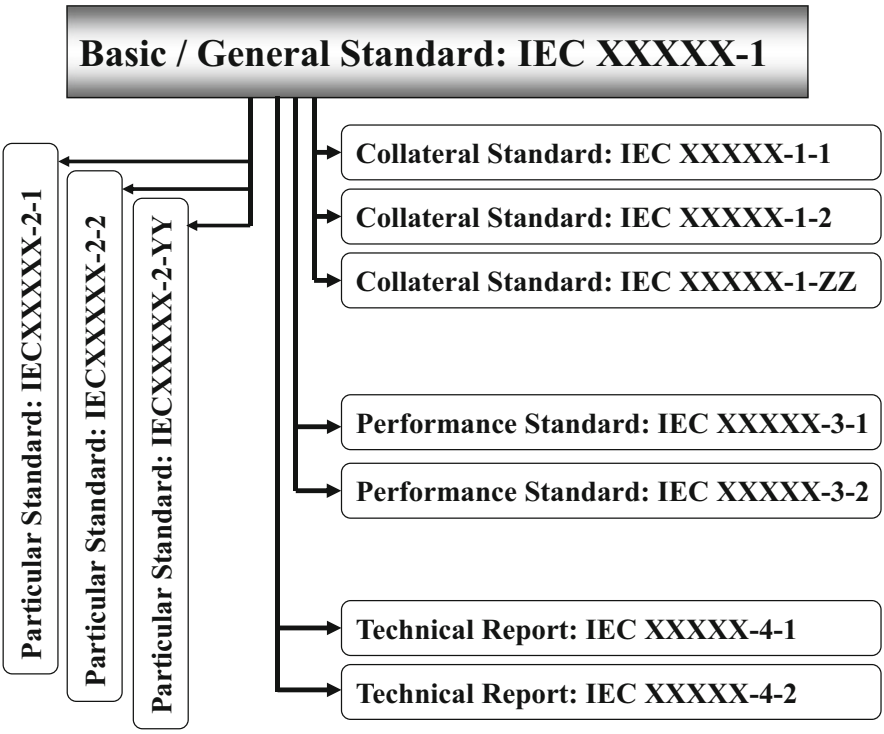

Fig. 4.4 General view of structure and naming of IEC standards

The most extensive family of medical device standard is the 60601 (Fig. 4.5), which addresses the safety and effectiveness of medical electrical equipment. The basic/general standard is formally known as IEC 60601-1—Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Compliance with this standard has become a de facto requirement for bringing new medical devices to market in many countries. The European (EN 60601-1) and Canadian (CSA 60601-1) versions of the standard are identical to the IEC standard.

There are also deviations from the standard that relate to country-specific requirements. Within IEC 60601-1, there are "collateral" standards that are denoted as IEC 60601-1-x; for example, IEC 60601-1-2 is the EMC collateral standard mentioned above. Other collateral standards include 60601-1-3, covering radiation protection for diagnostic X-ray systems, 60601-1-9 relating to environmental design, and 60601-1-11 recently introduced for home healthcare equipment. There are also many "particular" standards, denoted as IEC 60601-2-x that define specific requirements related to particular types of products, e.g. 60601-2-16 covers blood dialysis and filtration equipment.

The 60601 family covers several issues related to safety: electrical shock hazards and mean of protection; mechanical hazards (e.g. moving parts, pinching, crushing, over tilt, expelled parts, dropping, supports breaking); radiation hazards; ignition

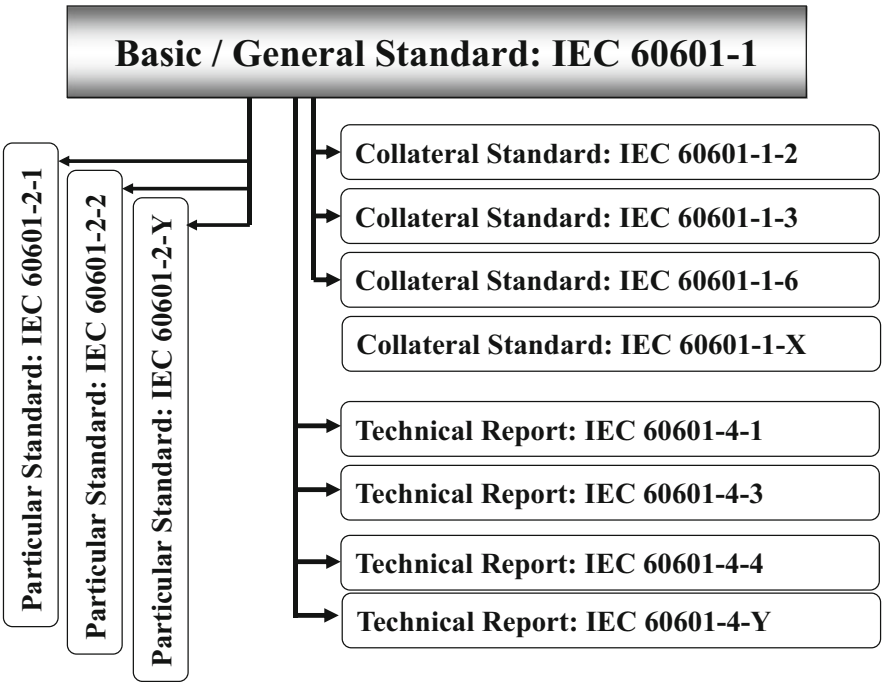

Fig. 4.5 Partial view of the 60601-1 family of standards

hazards of flammable anaesthetics; fire and other hazards; exposure to excessive temperatures, liquid spillage, pressure vessels, human errors and other such hazards.

Biological hazards (biocompatibility) are out of the scope of this standard, and are covered by the international standard family ISO 10993.

Sections 1 and 2 of IEC 60601-1 address the general requirements for tests (such as definitions and classification) and environmental conditions (including temperature, humidity, supply voltage and others). Section 9 identifies abnormal and fault conditions which must be evaluated. Section 10 addresses the general construction requirements for enclosure, components, and grounding (or earthing) that are not included in the other sections.

The up-to-date edition of this standard specifically calls out the Risk Management Process described in ISO 14971 that includes a risk management file where identifiable fault conditions are identified and assessed.

4.5.1 Harmonized Standards in Europe

In Europe, manufacturers working under the Medical Device Directives (MDD, AIMD or MDR) are given a legal "presumption of conformity" with essential

requirements if they apply harmonized standards as published in the Official Journal of the European Communities. Article 5 of MDD and AIMD state that "*member states must presume compliance with essential requirements if harmonized standards are applied*". In other words compliance with standards is voluntary, whereas essential requirements have the highest priority and must anyhow be fulfilled. In this context, standards are just one way to show compliance. If a manufacturer does not apply a harmonized standard, there is an obligation to document the solutions for fulfilling the essential requirements. The "presumption of conformity principle" is still present in MDR (Article 8).

4.5.2 Harmonized Standards in the USA

Whilst manufacturers are encouraged to use FDA-recognized consensus standards in their premarket submissions, conformance is voluntary. Demonstrating conformity with FDA-recognized standards facilitates the premarket review process. Standards that have been recognized by the FDA (either wholly or in part) are maintained and are searchable in the FDA's Recognized Consensus Standards database [14]. Standards for which a non-recognition determination has been made are listed in the Non-Recognized Standards database. A manufacturer may not declare conformity to a non-recognized standard.

Conclusion

The term "medical device" covers a very wide range of products, such as instruments, software and materials. Although the definitions of medical device may differ among national legislations, most of the definitions are based upon two principles: the medical purpose (i.e. the use for diagnosis, prevention, monitoring and treatment of disease) and the mechanism of actions (i.e. not based on pharmacological or metabolic or similar means). The classification of medical devices is a "risk-based" system based on the vulnerability of the human body taking account of the potential risks associated with the devices. Despite global efforts to harmonize regulation of medical devices via groups such as the Global Harmonization Task Force (GHTF), and the International Medical Device Regulators Forum there is a huge discrepancy among regulatory requirements all over the world.

In addition, technical standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand. Standards can be particularly valuable as they reflect the state of the art and reflect the best experience of industry, researchers, consumers and regulators worldwide.

Take Home Message

- The term *medical device* covers a very wide range of products, such as instruments, software and materials. Most of the definitions applied in the local regulations are based upon two principles: the medical purpose and the mechanism of action.
- The classification of medical devices is a "risk-based" system founded on the vulnerability of the human body and taking into account of the potential risks associated with the devices. The adopted criteria for this evaluation include parameters like duration of contact with the body, degree of invasiveness and local vs. systemic effect.
- In Europe, an important step is the introduction of the EU-MDR which includes, among others, new strict requirements as the identification of the responsible person for regulatory compliance, the implementation of the unique device identification (UDI) for better traceability and recall and the rigorous surveillance by Notified Bodies to reduce risks generated by unsafe devices.
- Technical standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand.

References

1. Global Harmonization Task Force (2012) Definition of the terms medical device and in vitro diagnostic (IVD) medical device. World Health Organization, Geneva. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf. Accessed Aug 2020
2. Global Harmonization Task Force (2012) Principles of medical device classification. World Health Organization, Geneva. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf. Accessed Aug 2020
3. 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
4. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
5. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market
6. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
7. Manual of Borderline and Classification in the Community Regulatory Framework for Medical Devices. Version 1.22 (05-2019). https://ec.europa.eu/docsroom/documents/33704. Accessed August 2020
8. MEDICAL DEVICES: Guidance document—Classification of medical device—MEDDEV 2. 4/1 Rev. 9 June 2010

9. CFR—Code of Federal Regulations Title 21—Food and Drugs—Chapter I—subchapter h medical devices. https://ecfr.federalregister.gov. Accessed Aug 2020
10. Product Classification Database. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm. Accessed Aug 2020
11. Government of Japan. Pharmaceutical Affairs Law (PAL). 1960 Act No. 145
12. Government of Japan. Pharmaceuticals and Medical Devices Act (PMD Act). 2013 Act No.84. [13] Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices. IMDRF Good Regulatory Review Practices Group. 31 Oct 2018. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf. Accessed Aug 2020
13. International Electrotechnical Commission. Developing International Standards. http://www.iec.ch/about/activities/standards.htm?ref=home. Accessed Aug 2020
14. Recognized Consensus Standards Database. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. Accessed Aug 2020