Chapter 11
Clinical Validation of the Medical Devices: A General Prospective

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11.1 Introduction

Medical devices are a key component in modern-day health care for a better quality of life. Medical devices are employed for a wide range of applications, including simple medical examinations such as thermistors and stethoscopes to highly sophisticated devices like artificial pacemakers and vascular stents [1, 2]. As defined by Global Harmonization Task Force (GHTF) the term "medical device" means ". . .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) of diagnosis, prevention, monitoring, treatment or alleviation of disease or diagnosis, monitoring, treatment, alleviation of or compensation for an injury or investigation, replacement, modification, or support of the anatomy or of a physiological process or supporting or sustaining life or control of conception or disinfection of medical devices or providing information for medical or diagnostic 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 by such means. . ." [3].

The medical device regulations are highly needed to contain the devices with poor quality as drugs. However, except for developed countries, very few countries follow strict regulations [4, 5]. Therefore, there is a compulsion to draft regulatory policies for all other countries to examine the quality, safety, and efficacy of medical devices before entering the market. Countries' dissimilar regulations on medical devices obstructed access to high-quality, safe, and efficacious medical devices to

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the end-users. Hence, there is a need to homogenize regulations to curtail the hurdles to enter the device in various markets. Among all, clinical validation's regulatory guidelines are the utmost important aspect to scrutinize the safety, quality, and efficacy of the medical devices.

In simple terms, clinical validation means the process of justifying all the clinical assessment study reports related to the device's performance, quality, safety, and efficacy with the regulatory compliance of any targeted markets. Usually, the final clinical validation is done by the highest regulatory authority of those countries. However, the need and types of clinical validation vary from device to device or class to class. The process of clinical confirmatory is a never-ending procedure for high risk associated devices, as per the implementation of post marketing clinical follow-up (PMCF), post-market surveillance (PMS), and periodic safety update report (PSUR) by the regulatory authorities of various countries. In recent days, various regulatory bodies have included another important regulation related to software across the globe. So, in a broader prospect, the clinical validation process for the clinical investigation plan and its results become mandatory regulatory compliance for every device.

Key Definitions Related to Clinical Validation (According to Indian MDR, 2017)

1. **Investigational medical device:** "A medical device (i) which does not have its predicate device or (ii) which is claimed for the new intended use or new population or new material or major design change; and is being assessed for safety or performance or effectiveness in a clinical investigation."
2. **Predicate device:** "A device, first time and first of its kind, approved for manufacture for sale or import and has the similar intended use, material of construction, and design characteristics as the device which is proposed for a license."
3. **Clinical evidence**: Defined as "(i) An in vitro diagnostic medical device, is all the information derived from a specimen collected from a human which supports the scientific validity and performance for its intended use; (ii) a medical device, the clinical data and the clinical evaluation report that supports the scientific validity and performance for its intended use."
4. **Clinical investigation**: "The systematic study of an investigational medical device in or on human participants to assess its safety, performance, or effectiveness."
5. **Clinical investigation plan**: "A document which contains the information about the rationale, aims and objective, design and the proposed analysis, conduct, methodology including performance, management, adverse event, withdrawal and statistical consideration and record-keeping pertaining to clinical investigation."
6. **Clinical performance evaluation:** "The systematic performance study of a new in vitro diagnostic medical device on a specimen collected from human participants to assess its performance."

7. **Clinical benefit:** "The positive impact of a device on the health of an individual, expressed in terms of a meaningful, measurable, patient-relevant clinical outcome (s), including outcome(s) related to diagnosis, or a positive impact on patient management or public health' as per the article 2(53) of the MDR."

A special wing of USFDA, i.e., Center for Devices and Radiological Health (CDRH), is accountable for regulating the manufacture, sale, distribution, re-label, and/or import of medical devices to the USA. According to USFDA, the devices are classified into three classes, i.e., Class I, II, or III, based on the risk associated with the devices. Class I devices possess no risk to the user's life, and thus they are subjected to some common controls and least regulations. Class II devices require some special controls and the general controls for receiving the market approval. Class III devices are those that support and sustain human life [6, 7]. Hence, it requires the demonstration of safety and efficacy through clinical trial studies before entering the market.

European Union (EU) acquires a decentralized system to achieve the marketing authority for the medical devices. Notified bodies in the EU acquire the quality assurance certificate and confirm post-approval obedience to quality management system (QMS) [6, 7]. Medical devices are classified and regulated by their respective country regulatory bodies to ensure their safety and efficacy before being commercialized. EU classifies devices into three main classes, i.e., Class I, IIa, IIb, and III depending on the risk. The device classification criteria are the duration of the contact, source of energy for the device, and the invasiveness of the device. Brief classification is presented as follows with some examples:

Class I: Hospital bed and blood pressure cuff
Class IIa: Hearing aid and X-ray diagnostic device
Class IIb: Ventilator and blood bags
Class III: Drug-eluting coronary stents

Various directives regulate the safety and marketing of medical devices in Europe, such as the Medical Device Directive (MDD 93/42/EEC), Active Implantable Medical Device Directive (AIMDD 90/42/EE), In vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EC), etc.

In India, the medical device section of the Central Drugs Standards Control Organization (CDSCO) acts as the highest regulating authority for medical devices and in vitro diagnostic. The CDSCO controls the medical device regulations through the Central Licensing Authority (CLA) and State Licensing Authority (SLA). Under the third schedule of MDR, notified bodies shall be registered with CDSCO and shall be audited by CDSCO and accredited by NABCB (National Accreditation Board for Certification Bodies) or Quality Council of India (QCI). According to Indian MDR 2017, the medical devices and in vitro diagnostics are classified into four classes (Class A, B, C, and D) under the new framework MDR 2017, where Class A and B shows the least risk and Class C and D devices show the higher risk to patients. The new framework was darted in consideration with USFDA and EU-MDR. The notified bodies and SLA are responsible for regulating and verifying the QMS of

Table 11.1 The recalled medical devices in various markets through clinical validation [9]

Name of the devices	Manufacturer	Recalled country	Date of Recall	Reason for recall
Dual-chamber pacemakers (Adapta™)	Medtronics	USA	January 2019	Due to circuit failure
Cardiac resynchronization therapy defibrillators (CRT-ds)	Abbott	USA	August 2017	Due to premature battery depletion complaints caused by lithium deposition
Chemolock™	ICU Medical	Worldwide	February 2019	Due to the presence of plastic burr
Continuous glucose monitoring (CGM) systems	Dexcom	USA	February 2016	Due to a faulty auditory alarm
8100 model Alaris pump modules along with air-in-line (AIL) sensor kits	Becton Dickinson's subsidiary carefusion	CANADA	December 2016	Due to faulty alarm
Catheters with Beacon® tip technology	Cook Medical	USA	April 2016	Polymer degradation of the catheter tip
Vial2Bag fluid transfer systems	West Pharmaceutical	Worldwide	January 2019	Due to functioning issues
Leadcare blood lead testing systems	Magellan Diagnostics	Worldwide	May 2017	Gives inaccurate test results

Class A and B devices. The CLA is responsible for checking and granting import or manufacturer licenses for Class C and D. The permission for conducting the clinical investigation should be taken from CDSCO in the respective form. It is also notifying that CLA can cross-check and verify all the clinical evidence and other QMS compliances of any class of device, a sale in the Indian market. According to the MDR provisions, the approval for clinical investigation plan, device performance report should be done by the CLA and PMS should be done by the manufacturer but should be verified by the CDSCO at the time of audits.

The strong regulatory guidelines of medical devices can drive the development of quality devices, among the clinical validation process is the key paramater. A clinical trial sponsor typically performs clinical validation to facilitate the development of a new product. The goal of clinical validation is to demonstrate the device acceptably identifies, measures, or predicts the clinical, biological, physical, functional state, or experience in the defined context of use [8]. In simple terms, the entire procedure provides a legal defense against the malpractices on the medical devices. In this chapter, we will discuss required clinical validation protocols and detailed procedures for validation in contrast with safety and type of device (new or existed similar device). Apart from this, the reader will also get an idea about validation procedures in various countries by their classes. Table 11.1 shows some of the recent recalled devices went through the clinical validation in various markets.

11.2 What Is Clinical Evaluation?

11.2.1 Definition

"Clinical evaluation is the systematic approach for assessing and analyzing clinical data by conducting the literature search of scientific data and/or by conducting the clinical trial of medical devices. Clinical evaluation is mandatory for the compliance of safety, clinical performance, and effectiveness [8, 10]."

There is always a great confusion between clinical evaluation and clinical trials (clinical investigation). The clinical trial is one of the clinical evaluation steps, whereas clinical evaluation requires final verification and validation of medical devices [11]. Generally, the clinical evaluation is dependent on the design and innovativeness of the medical device. For instance, if the device has a similar configuration as the available marketed product, it is also known as substantially equivalent devices and does not require clinical investigation [8, 10]. Suppose the device is predicted to substantially equivalent devices, e.g., a bone screw or cardiac stents. In that case, the clinical evaluation will be carried out from the literature search by identifying the scientific data that supports the devices' safety, efficacy, and performance. If data meets the device's desirable safety, efficacy, and performance, then the device is suitable for use.

While innovative medical devices require to prove their performance and safety by conducting the clinical investigation on the human subjects to prove the claims of intended applications [10].

11.2.2 Pre-Clinical Evaluation

Pre-clinical evaluation is a primary assessment of the device for safety and efficacy, including before the clinical investigation [12].

Pre-clinical evaluation of medical devices consists of the various examination of the devices according to standards like ISO 10093 and ASTM F748. Some of the evaluations are physicochemical characterization, in vitro cytotoxicity, irritation, skin sensitization, intra-cutaneous reactivity, material pyrogenicity, systemic toxicity, and implantation test genotoxicity, carcinogenicity, reproductive toxicity [8, 13].

Pre-clinical evaluation of medical device classification is a risk-based class requirement. Table 11.2 represents the categories of the devices and related evaluation [8].

Table 11.2 Pre-clinical test requirements of medical devices in contrast to their nature of contact and duration

Medical device categorization			Endpoints of biological evaluation														
Nature of body contact		**Contact duration**	**Physical and/or chemical information**	**Cytotoxicity**	**Sensitization**	**Irritation activity**	**Material mediated pyrogenicity**[a]	**Acute systemic toxicity**[b]	**Subacute toxicity**[b]	**Subchronic toxicity**[b]	**Chronic toxicity**[b]	**Implantation effects**[b,c]	**Hemocompatibility**	**Genotoxicity**[d]	**Carcinogenicity**[d]	**Reproductive/ developmental toxicity**[d,e]	**Degradation**[f]
Category	**Contact**	A – Limited (≤24 h) B – Prolonged (≥24 h to 30 d) C – Long term (>30 d)															
Surface medical device	Intact skin	A	N[g]	Y[h]	Y	Y											
		B	N	Y	Y	Y											
		C	N	Y	Y	Y											
	Mucosal membrane	A	N	Y	Y	Y											
		B	N	Y	Y	Y		Y	Y			Y					
		C	N	Y	Y	Y		Y	Y	Y	Y	Y		Y			
	Breached or compromised surface	A	N	Y	Y	Y	Y	Y									
		B	N	Y	Y	Y	Y	Y	Y			Y					
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y		
Externally Communicating medical device	Blood path, indirect	A	N	Y	Y	Y	Y	Y					Y				
		B	N	Y	Y	Y	Y	Y	Y				Y				
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
	Tissue/ bone/ dentin[e]	A	N	Y	Y	Y	Y	Y									
		B	N	Y	Y	Y	Y	Y	Y			Y		Y			
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y		
	Circulating blood	A	N	Y	Y	Y	Y	Y					Y	Y[i]			
		B	N	Y	Y	Y	Y	Y	Y			Y	Y	Y			
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		
Implant medical device	Tissue/bone[j]	A	N	Y	Y	Y	Y	Y									
		B	N	Y	Y	Y	Y	Y	Y			Y		Y			
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	Y		

	Blood	A	N	Y	Y	Y	Y	Y				Y	Y	Y			
		B	N	Y	Y	Y	Y	Y	Y			Y	Y	Y			
		C	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		

[a]ISO 10993-11:2017, Annex F

[b]Data extracted from assessments that include acute systemic toxicity, subacute toxicity, subchronic toxicity, and/or chronic toxicity may be sufficient if sufficient animals and time points are included and evaluated. Therefore, these studies are not always mandatory for acute, subacute, subchronic, and chronic toxicity

[c]Site specific implantation should be considered

[d]The carcinogenic, mutagenic, and/or toxic to reproduction prone medical devices (material) should be considered in the risk assessment

[e]Needs to assess reproductive and developmental toxicity of novel materials and medical devices with relevant target populations (e.g. pregnant women) and/or where there is the high risk potential for reproductive organs

[f]Degradation analysis required to generate for any medical device, component of medical device, and materials remaining within the patient

[g]N denotes prerequisite examination needed for a risk assessment

[h]Y denotes endpoints to be evaluated in the risk assessment

[i]All devices intended for extracorporeal circuits

[j]Medical devices contact with tissues, contain tissue fluids or subcutaneous spaces need to be tested as per device-specific standards for biocompatibility examination

11.3 Needs of Clinical Evaluation of Medical Devices

The clinical evaluation is the regulatory requirement of a device to enter into a market. Each country has its guidelines for the assessment of the safety and effectiveness of the devices.

Regulatory requirements like in India, Medical Devices Rules (MDR) 2017; USA, Code of Federal Regulations Title 21 (USFDA); Europe, European Commission; United Kingdom, Medicines and Healthcare Products Regulatory Agency; Japan, Pharmaceutical and Medical Devices Agency; Australia, Therapeutic Goods Administration, Global-International Organization for Standardization (ISO 13485, ISO 14155), etc. should follow to enter their respective markets [11]. The basic needs of clinical evaluation are to prove the medical devices' safety and performance by conducting the clinical evaluation either by scientific or clinical investigation data. Intended use of a new device possesses specific claim like unique features toward the application needs to prove the performance by full clinical investigations. Various markets have their documented norms for clinical investigations and some are listed below:

- India, MDR 2017, manufacturers have to submit clinical evidence to demonstrate the conformity of the essential principle of design.
- USFDA manufacturers need to submit clinical equivalence by scientific data by literature or conducting a clinical trial as per ISO 14155.
- EU, Medical Device Directives 93/42/EEC manufacturers need to conduct the clinical evaluation by literature or perform the clinical investigation as requirements of MEDEV 2.7 rev.4.followed by ISO 14155.
- Japan, Pharmaceutical Affair Law (PAL) needs to conduct the clinical evaluation by literature or perform clinical investigations as PAL requirements.
- ATG, administration needs to conduct the clinical evaluation by literature or perform clinical investigations.

For innovative medical devices, it needs to conduct the clinical investigation to understand the safety, performance, and effectiveness. A device similar to marketed product may not need to perform any clinical investigation since predicated data is available based on the physicochemical, biological, and technological characteristics. For instance, a newly developed device with unique design features and functions needs clinical investigation in human subjects (ISO 14155) to prove its performance and safety.

11.4 Type of Clinical Evaluation

11.4.1 Clinical Investigation

Clinical investigation of medical devices is classified into two distinct types: clinical trials (clinical investigation) and clinical evaluation by literature data. Clinical trials

are classified into two more categories based on the study's nature, i.e., pilot and pivot studies. Whereas the clinical evaluation is performed by collecting and analyzing the data published in the literature.

Clinical investigations are the regulatory requirements for developed medical devices. The clinical investigation for the devices is performed when sufficient scientific data is not available for particular medical devices. Moreover, the predicate medical devices must prove the devices' safety and effectiveness [12, 14, 15].

For instance, according to USFDA, for newly developed pacemakers or cardiac stent drug-eluting stent requires clinical evaluation with clinical trial data before releasing the products. Besides this, all high-risk Class III devices require clinical trial in the USA as regulatory requirements PMA (premarket approval) of USFDA. Similarly, the EU also requires clinical investigations to prove the safety and effectiveness of high-risk devices [16].

Steps Involved in Clinical Investigations

There are several steps involved in the clinical investigation of the new medical devices, Fig.11.1. The process of clinical investigation of the new medical devices is summarized as follows:

- The newly developed device, which does not have similar legally marketed devices, needs to prove its characteristics like clinical indication and intended purpose, technical—specification, design and biological—biocompatibility, etc.
- To define the plan for clinical evaluation
- Identification of the clinical data from the literature search or a clinical experience. The data could be either published or unpublished.
- Appraisal of data sets by scientific validity, suitability, demonstration of safety, clinical performance, and/or effectiveness of clinical data. Also, sample size, inclusion–exclusion criteria concerning age, medical condition, severity, prognostic factors, etc. Follow-up and outcome of the clinical data.

  Analysis of clinical data: a literature review of clinical data by using different analysis methods like sound methods, comprehensive analysis, additional pre-clinical evaluation, and clinical investigations or other measures is required for safety, effectiveness, and risk/benefit analysis.
- Is this clinical evidence sufficient to declare conformity with relevant essential principal consideration of novelty of device, risk level, and risk–benefit analysis?
- If yes, these are fulfilling all essential principal requirements, then no further clinical data needed (clinical investigation not needed).
- If no, these are not fulfilling all essential principal requirements, then additional clinical data required.
- Is the additional data available? If yes, then generate the new or additional data by the literature search; if no, then conduct the clinical investigation.
- Clinical investigation is needed to declare the safety and effectiveness of the device. Clinical investigation steps are:
  - Sponsor of clinical investigation
  - Institute performing the clinical investigation

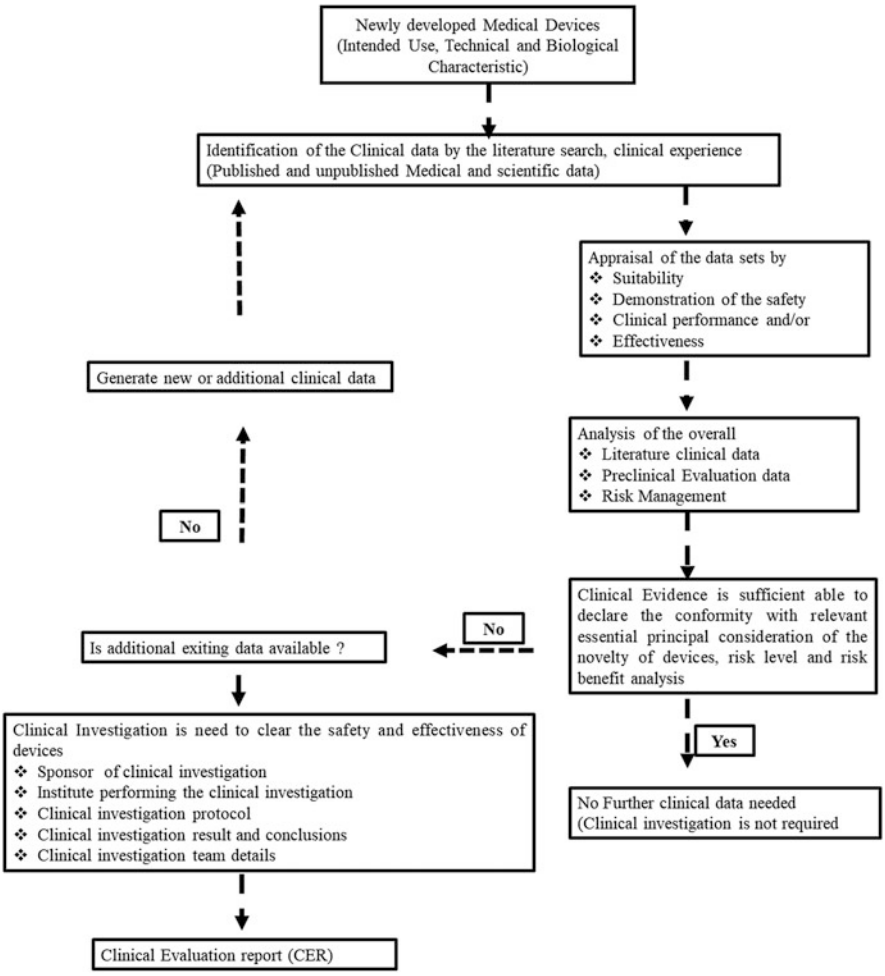


Fig. 11.1 The steps involved in the clinical investigation of new medical devices

  - Clinical investigation protocol (objectives, subjects, methods)
  - Clinical investigations results and conclusions
  - Clinical investigation team details

- Finally, the clinical evaluation report concludes the fate of the device by considering safety and effectiveness.

11.4.2 By Literature Way

Clinical evaluations by literature way are also regulatory requirements for substantially equivalent devices. The safety and effectiveness can be established by

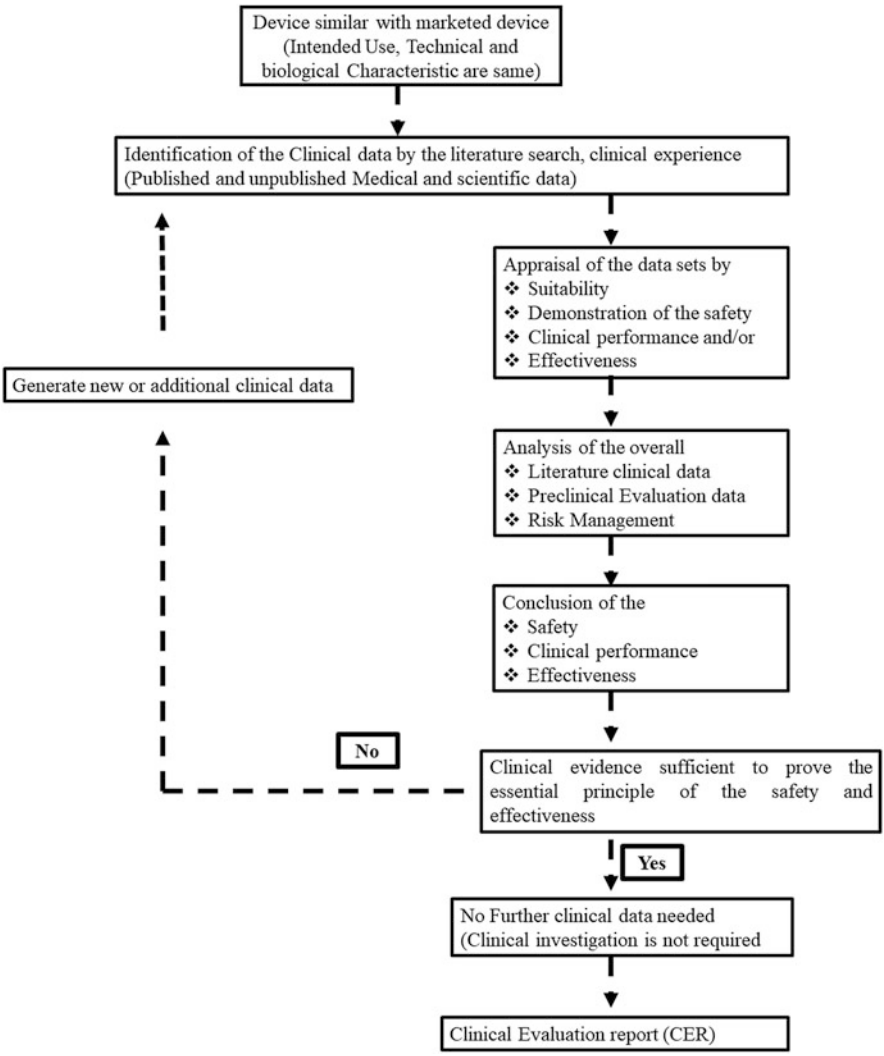


Fig. 11.2 The steps involved in the clinical investigation of the medical devices by literature route

conducting a literature search related to available clinical data (published and unpublished medical-scientific data) of exited devices. When predicate clinical data is insufficient, it needs to pass in clinical investigations for safety and effectiveness [10, 17]. The detailed flow of evolution is presented in Fig. 11.2.

Class II or lower-risk devices like wound dressing devices (hemostatic) or bone fixation devices (screws) do not require clinical trial, but it should be clinically equivalent as that of existing one [16].

Steps Involved in Clinical Evaluation by Literature Way

- The developed device is similar to legally marketed devices with characteristics such as clinical characteristic—indication and intended purpose, technical characteristic—specification and design, biological characteristic—material biocompatibility.
- Define the plan for clinical evaluation **Identification of the potential threat from the previous research** works and clinical experience from published and unpublished clinical data.
- Appraisal of data sets by scientific **justification**, suitability, **criteria** of safety, clinical performance, and/or effectiveness of clinical data. Besides, sample size, inclusion–exclusion criteria concerning age, medical condition, severity, prognostic factors, etc. Follow-up and outcome of the clinical data.
- Analysis of clinical data: a literature review of clinical data by using different analysis methods like sound methods, comprehensive analysis, additional pre-clinical evaluation, and clinical investigations or other measures is required for safety, effectiveness, and risk/benefit analysis. Besides, it needs to determine the post-market clinical follow-up when any risk remains from risk analysis and then describe residual risks and any other information.
- The gathering of clinical evidence is sufficient to prove the essential principle of safety and effectiveness.
- Is this clinical evidence sufficient to declare conformity with relevant essential principal consideration of intended use, risk level, and risk–benefit analysis?
- If yes, these fulfill all essential principal requirements, then no further clinical data is needed to complete a clinical evaluation report.
- If no, these are not fulfilling all essential principal requirements, then additional clinical data required.
- Generate new or additional data or conduct the clinical study.
- Prepare a clinical evaluation report.

The devices are developed based on the predicated devices so that all the characteristic features should be similar to predicates devices. The specifications such as clinical indication, technical performance, design, and biological aspect must be similar to that of the predicate devices.

Make a clinical evaluation plan and define the scope, contents of the clinical evaluation like description and characteristic of device, clinical background state of the art, whether the device under evaluation and clinical equivalence, identification, analysis, and appraisal of clinical data. Further, it needs to document the summary of clinical data, safety-related data, and conclusion.

Identification of clinical data from databases like PubMed, Medscape, Prospero, Cochrane, Clinical Trials database, incident report on the MAUDE database, DAEN, and MHRA database by defining the search term or defining keyword.

Analysis of clinical data—literature clinical data review by using different analysis methods like—sound methods, comprehensive analysis, additional pre-clinical evaluation, and clinical investigations or other measures are required for safety, effectiveness, and risk/benefit analysis, determine needs of the post-market clinical follow-up when any risk is remaining from risk analysis, then describe residual risks any other information.

Inclusion–exclusion criteria concerning age, medical condition, severity, and prognostic factors, etc. Follow-up and outcome of the clinical data.

Final appraisal of data sets by scientific validity, suitability, demonstration of safety, clinical performance, and/or effectiveness of clinical data. Appraisal criteria are based on level 1, level 2, level 3 data.

If clinical evidence from the literature is sufficient to prove the essential principle of safety and effectiveness of the devices, then no further clinical data needed to complete the clinical evaluation report. Whereas if data fail to prove the principle requirement, then need to generate the new additional data or perform the clinical trial and generate the clinical evaluation report. Figure 11.2 depicts the overall process of literature route for the clinical investigation of medical devices.

11.5 Clinical Validation According to the Type of Devices

11.5.1 Clinical Validation

Clinical validation of medical devices will be carried by their application with consideration of their risk factor. The classification of medical devices will majorly rely on the safety of the end-user. The major markets classified the medical devices in almost the same fashion with consideration of risk and named differently. Based on the devices' classification, the regulation is formulated for clinical validation to understand the safety and efficacy before entering into the market. Understanding clinical validation of medical devices by class is essential and here, the validation procedure is presented based on USFDA.

According to the Clinical Laboratory Improvement Act (CLIA) of the USA, Validation is the confirmation by investigation and provision of objective evidence that proves the medical device meets the user's need and intended use [18].

The validation can be classified as:

I. Process validation: It must be conducted before the production to ensure that the devices' manufacturing procedure does not affect the overall safety and performance of the devices.
II. Design validation: It must be completed before delivering the product to ensure that the device confirmation or the handling does not affect the device performance.

It is also remembered that the route of process validation and design validation changes from country to country as well as device to device, as medical devices are

used for a wide range of applications. Here we tried to give a glimpse of the process: design validation and in vitro diagnostics as taking the USA as a reference.

11.5.2 Process Validation

Process validation is defined in the FDA's 21 CFR part 820 (quality system regulation) subpart (G) 820.75. Process validation is defined as establishment of evidence for an objective by a process that consistently produces a result to meet predetermined specifications. The results of a particular process will be fully verified by subsequent inspections and tests. Prior to that, the process needs to be validated with a high degree of assurance and approved according to established procedures [18]. It must consider the key set of protocols with installation qualification (IQ), performance qualification (PQ), and operational qualification (OQ).

Regulatory Requirements for Process Validation
(a) Requirements of ISO 13485
(b) Further relevant national and international provisions: GHTF (now International Medical Device Regulators Forum (IMDRF))
(c) Requirements of the FDA (21 CFR part 820.75)

Key Points for the Control of Validated Processes
(a) Monitoring and control methods and data
(b) Date performed
(c) Individual(s) performing the process, where appropriate
(d) Major equipment used, where appropriate

Tips for Validating a Process
(a) Validate only relevant parameters
(b) Validating a validation process
(c) Verifying instead of validating
(d) Process validation and PQ, IQ, and OQ

11.5.3 Revalidation

It is a part of the process validation; whenever aberrations are observed in the processes of manufacturing, immediate review process is needed for the process validation.

Various validations are performed in process validation, for instance, prospective validation, concurrent validation, retrospective validation, and laboratory and pilot-scale validation.

(a) Prospective validation is a pre-planned validation.
(b) Concurrent validation is the data collected in a manufacturing facility during the actual study process.
(c) Retrospective validation is where the production has been started but has not been validated according to the prospective, and concurrent protocol is not a realistic option.
(d) Laboratory and pilot-scale validation: The planned manufacturing processes cannot be carried out in a manufacturing facility.

11.5.4 Design Validation

Design validation is also addressed by FDA's 21 CFR part 820.30, and additional details were specified in FDA's Design Control Guidance for Medical Devices [1].

Following nine criteria are required for design validation:

1. User friendly device designs and operations that are self-manifest and blunder proof.
2. Device safety, efficiency, working, and performance.
3. The variety of envisioned user populaces. These include the variety of users with miscellaneous physical properties and abilities (height, size, dexterity, flexibility, vision, hearing, and tactile compassion, etc.), cultural circumstances and languages, learning skills, and emotional and intellectual capabilities. The level of information and understanding and exercise can also affect how well a user can network with a specific medical device.
4. The planned patient populaces should contain neonates, children, young adults, adults, and the elderly.
5. They use surroundings, ranging from operating rooms (ORs), emergency rooms (ERs), to standard hospital rooms, clinics, and homes. The clinical atmosphere is an intricate system of medical and support personnel and patients. They can household a huge sum of diverse medical devices and supportive equipment. The surroundings in a clinical situation are well controlled related to the atmosphere of a home. Factors like humidity, temperature, vibration, noise, space, lighting, compatibility with other devices, radiofrequency interference, electrical-electromagnetic interference, and atmospheric pressure must be built into the design validation.
6. Clear, comprehensible IFUs that can be effortlessly followed and recollected when users return after an interval to use the device once more. Methods of directives must be geared toward intended user populaces. Electronic directions such as videos may be more effective for a certain demographic of users than the physical user manuals. Additionally, approaches to writing the directives, i.e., illustrative versus straight text, can also affect usability.
7. Efficacy of use can be measured by the total number of steps done acceptably divided by the total number of steps. This points to use errors and the frequency of those errors during use.

8. Efficiency of use can be obtained by the total time taken to complete the tasks versus a targeted goal.
9. User approval and acceptability of use for each task and the overall serviceability and operation of the device can be measured using the survey (questionnaires) with a Likert-type scale and subsequently analyzing it.

- **Software validation**: It is a part of the design validation of a finished product that confirms the intended use's software specifications.

The International Medical Device Regulators Forum (IMDRF) is a group of medical device regulators globally joined together to harmonize medical products' regulatory requirements that diverge from one country to the other. The World Health Organization (WHO) acts as an official spectator. The Asia Pacific Economic Cooperation (APEC), Regulatory Harmonization Steering Committee (RHSC), Life Sciences Innovation Forum's (LSIF), the Asian Harmonization Working Party (AHWP), and the Pan American Health Organization (PAHO) are the regional harmonization initiatives with IMDRF [19].

According to all the regulatory bodies and forums, medical devices' clinical validation and clinical evaluation come under Quality System (QS) regulation 21 CFR part 820.

11.6 Clinical Validation for each Class of Medical Devices

The following are common examples of processes that should be validated during the manufacturing of the medical device.

(a) Sterilization and sterile packaging sealing
(b) Cleanroom ambient conditions
(c) Aseptic filling
(d) Lyophilization
(e) Heat treating, plating, welding, soldering, painting, etc.
(f) Plastic injection molding

These are steps of validation involved in the processing of a medical device of all the three classes according to USFDA.

Class I
Class I devices are considered low-risk devices and are subjected to only general controls alone. The duration of device contact with the body is < 24 hours. Class I devices are mostly non-invasive devices. This class is exempt from premarket notification 510(k) and premarket approval (PMA). Examples of Class I medical devices include bandages, surgical instruments, wheelchairs, etc.

Class I medical devices are further divided into three classes: Class 1 s, 1r, and 1 m. This subclass of Class I medical devices requires 510(k).

(a) 1 s: Devices that are placed on the market in a sterile condition
(b) 1r: Reusable surgical instruments (r stands for "reusable")
(c) 1 m: Devices with a measuring function

If the medical devices fall under any of the subclass of Class 1 among 1 s, 1r, and 1 m, the device undergoes various clinical validation steps as mentioned in the GHTF, and it may also require 510(k) [20]. The clinical validation of medical devices step-by-step flow chart is shown in Fig.11.1.

Class II

Class II devices are considered as minimal risk devices and are subjected to general controls and special controls. The duration of device contact with the body ranges from 24 hours to 30 days. Blood collection tubes come under Class II devices; these are the minimally invasive devices. This Class II device requires premarket notification 510(k). Examples of Class II devices include infusion pumps for intravenous medication and computed tomography.

Often the blood collection tubes (BCTs) are underrecognized or ignored variable in the preanalytical phase of clinical laboratory studies. BCTs validation considerations are according to Clinical Laboratory Standards Institute (CLSI) GP34-A guidelines [21]. The clinical validation of Class II medical devices step-by-step flow chart is shown in Fig.11.1.

Class III

Class III devices include most of the implants, and these are considered high risk, which are subjected to the most stringent standards. Class III devices pass through number of pathways to reach the market for premarket approval (PMA) [22]. In this class, the implants or biomaterial intended to use will contact the body for more than 30 days; it would be regarded as high risk. Examples of Class III medical devices include a pacemaker, cardiac stents, brain stimulators, etc.

Joint prosthesis comes under the Class III high-risk devices category. The typical clinical failure scenarios reported for epiphyseal stem in joint prosthesis include aseptic loosening, mechanical failure, and sub-capital dislocation. It is essential to develop precise and reliable metrics to understand the functional aspects, which identify how well the patient recovered after the operation. Until then, the verdict of a claimed assistance's clinical relevance remains entirely on the clinical experts. However, it is the accountability of the pre-clinical validation to assess if the claimed benefit can be measured; if this is not the case, the introduction of a new design is unethical [23]. The clinical validation of Class III medical devices step-by-step flow chart is shown in Fig. 11.3. The clinical validation and clinical evaluation process are stringent in Class III medical devices as they fall under the high-risk category.

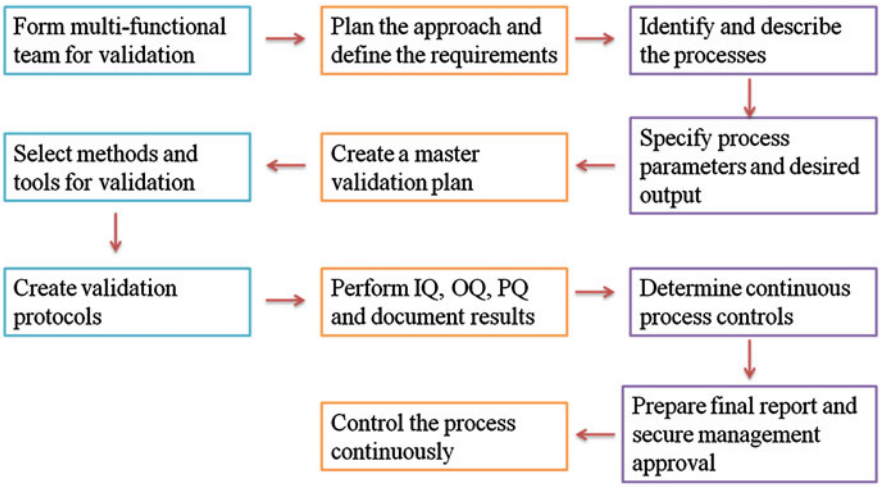


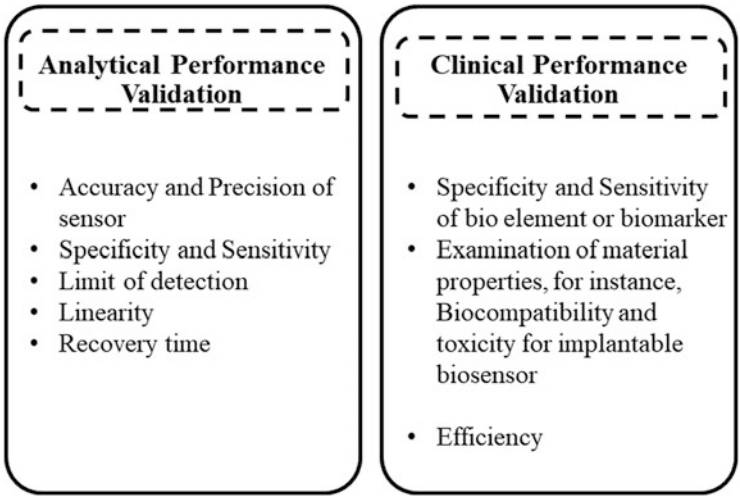
Fig. 11.3 Basic steps in medical devices process validation from GHTF

11.7 Clinical and Analytical Validations of Biosensors Based IVDs

In the twenty-first century, the biosensor based diagnostic devices open a new dimension for the manufacturer, as it gives rapid, high-throughput clinical data regarding the intended application [24]. Thus, the regulation and clinical validation of these types of devices become a general mandatory requirement to control and ensure the devices' safety and performance feasibility for launching them to the market. Biosensors are usually considered a diagnosing system to predict, measure, or monitor any physiological entity's presence or upregulation in terms of different signaling processes like electrical, optical, and thermal [25, 26]. According to the International Union of Pure and Applied Chemistry (IUPAC), the "biosensors" are defined as "a device that uses specific biochemical reactions mediated by isolated enzymes, immune-systems, tissues, organelles, or whole cells to detect chemical compounds usually by electrical, thermal or optical signals" [27]. Now, as per the 21 CFR 809.3 of USFDA regulation, the in vitro diagnostic products (IVD) are entitled to "reagents, instruments, and systems intended for use in the diagnosis of a disease or other conditions, including a determination of the state of health, to cure, mitigate, treat, or prevent disease or its sequelae" [28, 29]. Considering the above two definitions from the two well-established statutory bodies, one can consider that "biosensor" as an in vitro diagnostic product. Though there is no specified regulatory pathway that is reported for clinical validation of biosensors, some countries where the regulatory framework is deep-rooted regulate and validate biosensors' safety and clinical performance as per the in vitro diagnostic devices regulations. Besides that, some de facto agencies like the International Standardization Organization (ISO),

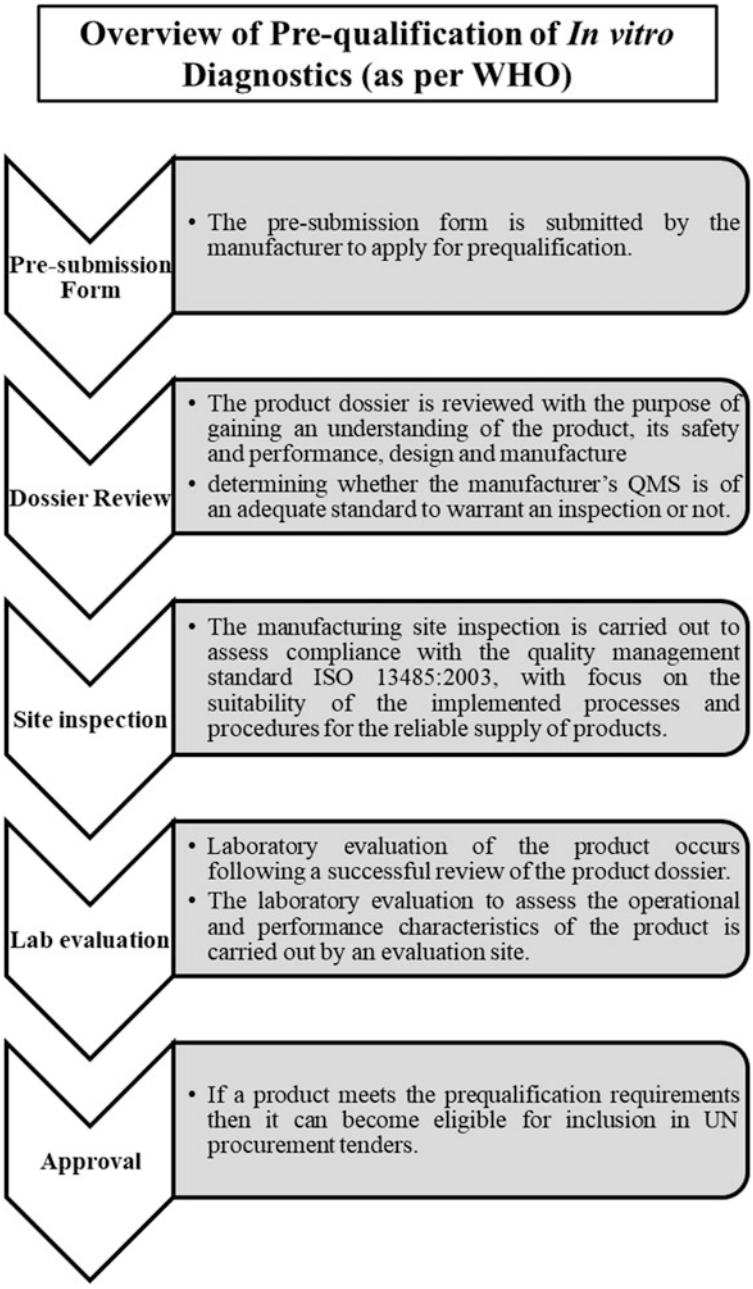
ASTM, IMDRF developed some regulations and strategies for controlling and validating biosensors' crucial parameters.

It is important to note that as the arena of biosensors is so-vast and their uses, detection strategies also versatile in nature, for that the ultimate clinical validation of these types of devices depends on their intended application, claimed analytical characteristics, and efficacy of detection systems [30]. The clinical performance evaluation procedure or validation of sensors is principally based upon the two main parameters, they are analytic performance validation and clinical performance validation [29, 31]. **The following illustration depicts the key considerations involved in the validation of biosensors.**



The projected value for each parameter correlates with a certain standard to satisfy or validate the product. ISO/TS 21412:2020 is one such standard that provides specification limits of characteristics and measurement methods of the materials associated with the electrochemical biosensors [32]. Another well-established standard is ISO/TR 19693:2018; this standard's scope is for characterization, the method, and strategies of surface functionalization of the silane-based group for sensing the biological elements upon paper-based or glass slides [33]. This particular standard is related to all those types of sensors where the sensor's surface is modified to immobilization or generation of electrical signals. One remarkable difference between the analytical performance validation of qualitative and quantitative sensor is that for qualitative sensors, the manufacturer or applicant should submit the evaluation report related to its specificity/sensitivity and limit of detection (LOD) only, whereas, for quantitative sensors, the applicant should submit all the reports accordance with sensitivity, specificity, LOD, accuracy, reusability, measuring range, etc. [34]In recent times, the World Health Organization (WHO) proposed some prerequisite requirements for the qualification of the in vitro diagnostic tests [35]. It ensures the safety and performance of the device and makes clinical data

more reliable to healthcare professionals. **The following illustration reflects an overall procedure of the pre-qualification program by the WHO** [36].



Recently, CDSCO classified the notified in vitro diagnostic devices into three categories: IVD analyzer (53 types), IVD instruments (18 types), and IVD software (9 types) [37]. According to this amendment, all the POC biosensors are regulated as IVD analyzers, as they analyze certain physiological biomarker levels. For other non-invasive wearable devices such as continuous glucose monitoring systems, two separate clinical evaluation reports are needed for the implanted part and software part, respectively. All the biosensors associated with any software or computer system should be regulated distinctively for the clinical validation of software as a medical device. For the other simple POC diagnostic systems, the applicant should submit a performance evaluation report issued by the central medical devices testing laboratory or a medical device testing laboratory registered under rule 83 or by any laboratory accredited by the National Accreditation Board for Testing and Calibration Laboratories or by any hospital accredited by National Accreditation Board for Hospitals and Healthcare Providers [38].

In conclusion, we can say that for the clinical validation of sensor-based diagnostic devices, both the analytical performance verification and clinical performance evaluation are necessary by following respective standards to demonstrate the overall performance and reliability of the sensor-generated data for commercialization of the product. Recently some regulatory bodies like USFDA, IMDRF proposed or encouraged the applicant or manufacturers to consult the tests' necessity and justify the results directly with the regulatory authority for faster and smooth commercialization of the product.

11.8 The Regulatory Perspective of the Medical Device in Consideration with Clinical Validation

11.8.1 Medical Device Rules (MDR)-2017, India

Medical devices are regulated as "drugs" in India. The CDSCO acts as the highest authority for the regulation of medical devices and in vitro diagnostic devices. The Government of India gazette two different notifications on February 11, 2020, for a revised definition of medical devices and the medical devices regulations (Amendment), 2020. Previously, only 37 types of medical devices were regulated or notified to be regulated in India. The revised regulations cover all medical devices to determine their quality, safety, and efficacy. According to the new medical device rules, Chapter VII, published by CDSCO, deals with medical devices' clinical investigation and clinical performance evaluation of new in vitro diagnostics. Several medical device testing laboratories have been developed to cross-check and ensure the products' quality, safety, and efficacy. The governing bodies of the MDR also enlisted rule 49 to rule 62 for the same. MDR also separates medical devices' guidelines into some accompanying legislation such as clinical investigation, import, manufacturing, sales, and distribution. Based on the device classification, the

requirement of a clinical investigation or testing protocols is also classified in a detailed manner. As per the MDR, Class A devices need the least clinical testing, and Class D devices require more accurate clinical validation data.

Chapter seven of MDR contains all the regulatory compliances required for getting the authorization to import or manufacture investigational medical devices for clinical studies. A few numbers of forms are also mandated to validate and control the clinical investigation. Some of the forms, namely MD-12, MD-16, MD-22, and MD-24, are mandatory to submit irrespective of device class. For getting the clinical investigation's approval, the application of Class A and B should be submitted to the State Licensing Authority (SLA) and for Class C and D to the Central Licensing Authority (CLA). All the application submission and the grant of permission/approval licenses are revised through the online portal of CDSCO (https://cdscomdonline.gov.in). All the required compliances for the Indian market are given in Fig.11.4. As per the Indian regulations, the clinical studies are carried out in two phases: the pilot and pivotal clinical investigations to validate safety and efficacy. The pilot clinical investigation is done for determining the preliminary device performance, checking the eligibility aspects and their applications. The pivotal study's goal is to determine the unavoidable adverse event, explore the device mechanism, and establish a process to determine an outcome measure. Pivotal studies have been mandatory for a new custom based investigational medical device that does not have a substantially equivalent device but gets approved for marketing in any country except India, to get the confirmation regarding the devices' performance upon the Indian ethnicity.

- **Submission of clinical data with the application**

1. Design analysis data including:
   (a) Documents of design input and design output;
   (b) Results of mechanical and electrical tests;
   (c) Reliability tests;
   (d) Authentication of device software;
   (e) Other performance tests (if any);
   (f) Ex vivo studies.
2. The agreement between the sponsor and principal and coordinating investigator (s).
3. The appropriate insurance certificate, if any.
4. Forms for reporting any adverse event and serious adverse event.
5. Report of biocompatibility tests along with the rationale for selecting these tests, including a summary report.
6. Results of the risk analysis.
7. Animal performance study data.
8. Clinical investigational plan, investigator's brochure, case report form, informed consent form, investigator's undertaking, and ethics committee clearance.
9. Pilot and pivotal clinical investigation data include clinical data that may carry out in other countries.

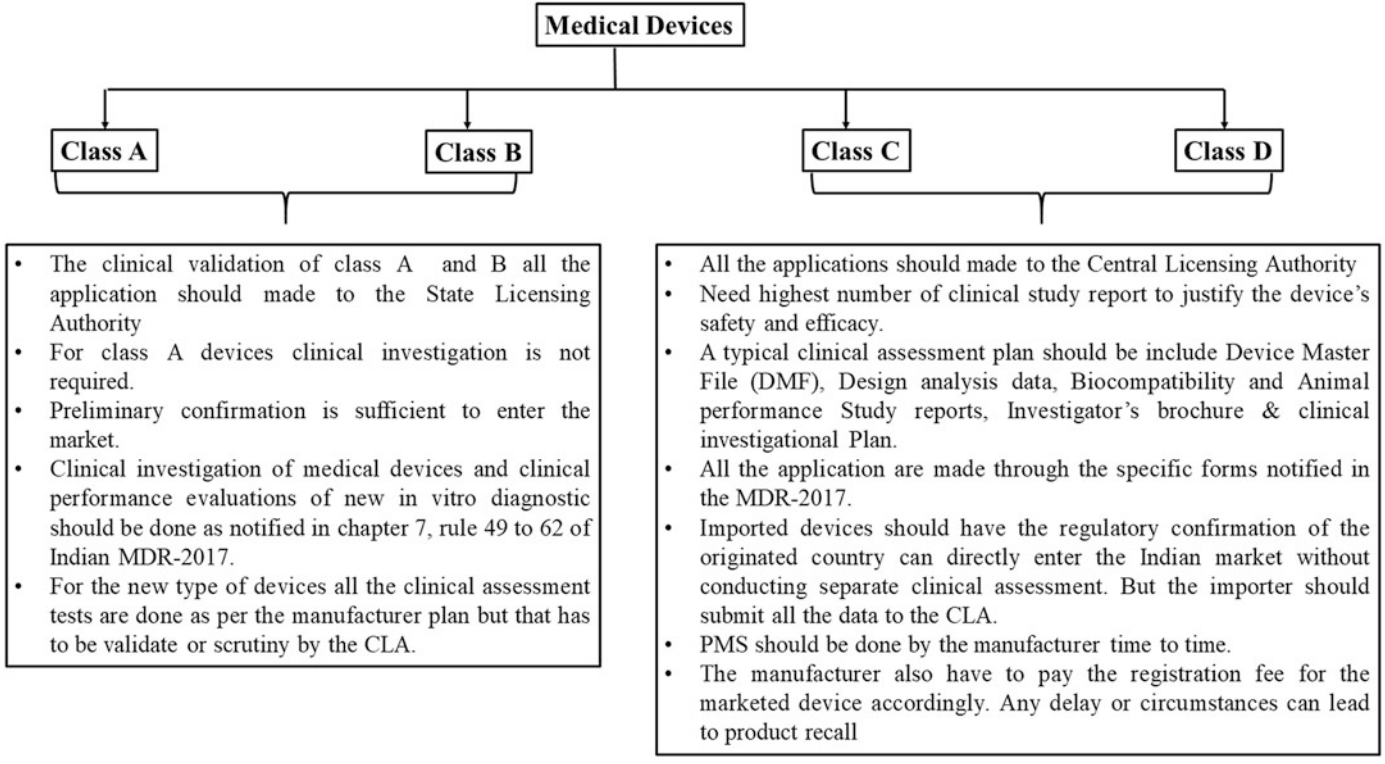


Fig. 11.4 Regulatory compliances required for the clinical validation of medical device in India as per the Indian MDR 2017

10. Regulatory status and restriction on use in other countries, if any, where marketed or approved.
11. Proposed instructions for use and labels.

The regulation is also implemented for the devices which contain drugs. If the drug is already approved or has proof of human safety, some clinical examinations can be skipped by the manufacturer.

MDR states that to perform the clinical evaluation of any devices, importers or the manufacturers will need to follow any of the performance standards imposed by the Bureau of Indian Standards (BIS) or given by the Ministry of Health and Family Welfare in the Central Government. It also proposed, where there are no pertinent standards recommended by BIS, then the manufacturer can do the clinical studies in accordance with the standards released by the International Organization for Standardization (ISO) or the International Electro-Technical Commission (IEC), or by any other standard agency. It also claimed that if no such standards have been found, then the manufacturer can design his protocol and validate it accordingly [39].

11.8.2 Food and Drug Administration USA

Within FDA, the Center for Devices and Radiological Health (CDRH) is primarily accountable for medical device regulation and clinical validation. According to the FDA's 3-tier risk-based classification, Class I devices are exempted from the clinical validation or the confirmatory assessment test; only the minimum device safety report has to be submitted. Class II devices have some amount of more risk factors than Class I, so these devices are needed some special concern about the packaging, labeling, user guidance along with the premarket notification (PMN), which is needed to market this product. Class III devices require the highest number of regulatory compliances regarding clinical validation and risk assessment testing. It is also suggested that any manufacturer or the sponsors can also validate the clinical testing data with any other internationally accepted standards for ensuring the device's safety and efficacy. In a proposal to CDRH, the FDA suggests that sponsors include their risk assessment at the start of the segment on biocompatibility testing. According to the FDA, it is also recommended that they have to give a proper reason for explaining any toxicities and adverse effects identified in their biocompatibility testing or other clinical evaluations study. As per the amendment of the CDRH, the manufacturers also follow some de facto standards to support their risk assessment program. Some of such standards like ISO 10993-5 "Biological evaluation of medical devices—Part 5: Tests for in vitro cytotoxicity testing, ISO 10993-18 "Biological evaluation of medical devices—Part 18: Chemical characterization of materials" or ISO/TS 10993–19 "Biological evaluation of medical devices—Part 19: Physio-chemical, morphological and topographical characterization of materials" must be followed for Class III devices [29]. All the essential compliance is given in Fig.11.5 for the USFDA clinical validation. However, the guidelines are well

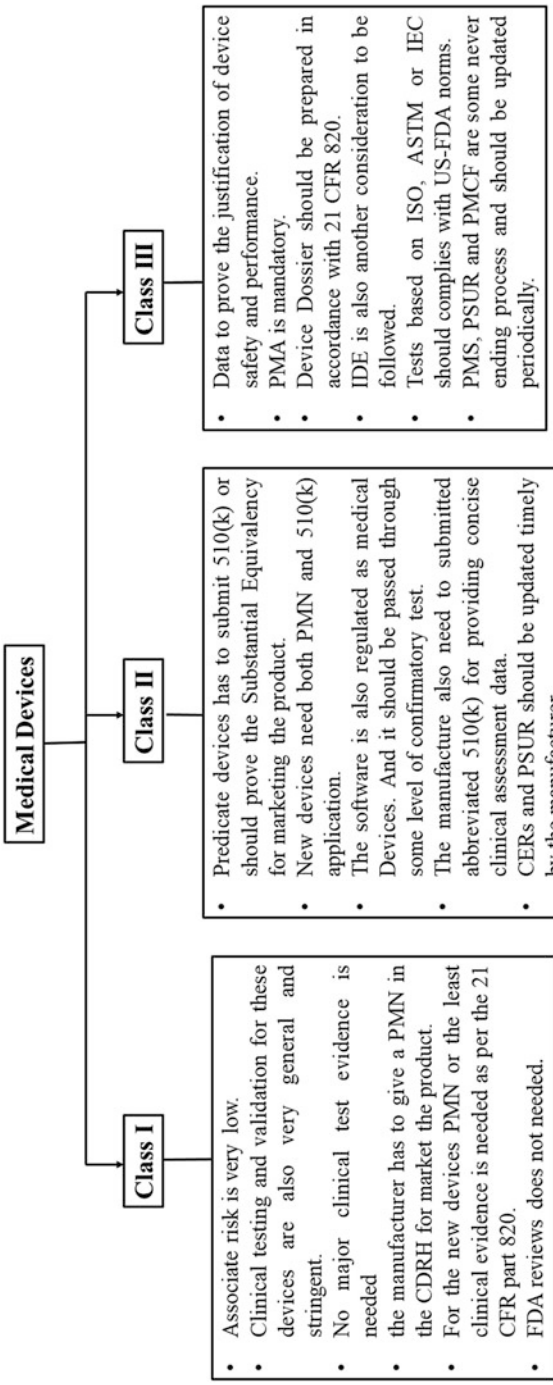


Fig. 11.5 The chart depicts the required regulatory compliances for the clinical validation as per the USFDA

designed for clinical validation of medical devices. However, it is essential to comply with the local (country) regulations to introduce a product. To support the safety validation, the explanation of selecting the standards and their protocols needs to provided so that the FDA can review the process. Generally, the FDA asks for the clinical evaluation data with their testing protocols related to device safety requirements [40].

Another mandatory clinical, regulatory compliance is PMS, which is needed for high-risk devices (i.e., Class II and III) after the FDA approval and marketing. The federal Safe Medical Devices Act of 1990 and the FDA Modernization Act of 1997 (FDAMA) permitted the FDA to required essential PMS for these classes of devices to obtain some goals such as reporting of any serious adverse events (SAE) or the device failure and tracking the devices or for the product recall.

As per the new amendment, for notifying the updated information regarding the device quality, safety, and efficacy, a Periodic Safety Update Report (PSUR) has to be submitted to the CDRH once after the market share devices [34]. **The PSURs should be updated every six months' interval for the first two years after the medical device's approval even more for the next two years.** For getting the clinical validation of a Humanitarian Device Exemption (HDE), the clinical pieces of evidence related to the device's effectiveness and lack of significant risk have to acquiesce with the HDE application. One of the main differences between the application of HDE and PMA is that in the case of HDE, the manufacturer only required the clinical shreds of evidence related to devising safety. However, for PMA, both the device safety and efficacy consideration are needed, from the point of clinical justification [41].

11.8.3 Medical Devices Clinical Validation Process in EU

In the EU, three medical device legislations have been implemented such as Medical Device Directive (MDD) 90/385/EEC for active implantable medical devices, MDD 93/42/EEC regarding medical devices, and directive of in vitro diagnostic medical devices 98/79/EC [16]. Considering these three MDDs, a new Medical Device Rules (MDR)-2017/745 (amendment) has been published for medical device regulation and MDR 2017/746 for in vitro diagnostic devices. The newly published MDR comprises 10 chapters, with 123 articles and 17 annexes, and it also covers all the clinical assessment tests and examinations for the EU certification, contingent upon the kind of support (commercial, non-commercial, and academic). Chapter 6 of the MDR deals with the clinical evaluation and their validation for the product aiming to market in the EU. By concerning MDD 93/42/EC, the lower-risk devices, i.e., Class I and IIa, should have Clinical Evaluation Reports (CERs) and higher-risk devices such as Class IIb and III, the manufacturer needed to compile clinical data on device dossier. The clinical evaluation should be conducted on MDR following Article 61 and Part A of Annex XIV [7]. Also, a public summary of safety and clinical performance (Article 32 of EU-MDR) must be submitted by the manufacturer for a

certain category of devices. To be precise, the manufacturer must have a documented plan to conduct a clinical evaluation, confirm conformity with general safety and performance requirements, evaluate for unwanted adverse effects, and estimate the benefit–risk ratio's acceptability Fig. 11.6 represents the neccessary documents for clincal assesment of Medical Devices under EU. Article 61 [1] of the MDR and Article 56 [1] of the IVDR state that "The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with relevant general safety and performance requirements." **Finally, a clinical evaluation assessment report (CEAR) authorized by the notified body is needed, which gives the inference of the clinical studies.** It is one of the core requirements of the Medical Device Regulation (EU) 2017/745 (MDR) [34].

The clinical evaluation results shall be documented in a Clinical Evaluation Report (CER), which should include the clinical data related to the evaluation of scientific literature, key findings of clinical investigations, and a consideration of available alternative key measures. It is also important to remember that the clinical evaluation and its documentation shall be updated throughout the device life cycle with clinical data obtained from PMCF and PMS. The EU-MDR also mandate Unique Device Identification (UDI) and European Databank on Medical Devices (EUDAMED) for tracing the ADE reporting and facilitating tracing of the device. EUDAMED is developed under the consideration of Article 33 of MDR. It was expected to go live on March 25, 2020, for an application on May 26, 2020. But as per the latest information from the EU is that EUDAMED will be delayed until May 2022. The authorities anyway planned this situation. If its implementation is delayed, the manufacturers will have six months to fill the database after working.

Another key component for the EU approval is CE certification of the products. By submitting CE certification with the other clinical evidence, the manufacturer can increase the device's safety, which is further help to get the final approval. CE certification also facilitated the customer preference and free movement of the product in the EU's respective countries. According to the new legislation of MDR 2017/745, the Medical Device Software (MDSW) also needs to be clinically validated with an intended purpose. It is also stated that if a software is controlling more than one medical device, an independent ***Clinical Evaluation (MDR) or Performance Evaluation (IVDR)*** is required for each predicted and clinically viable software-device combination [42].

11.8.4 Clinical Confirmatory Process in Australia

In Australia, the Therapeutic Goods Administration (TGA) regulates medical device registration, manufacturing, and sales. It also acts as a governing body for reviewing and updating the Australian Regulatory Guidelines for Medical Devices (ARGMD). As per Regulation 4.1 of the Therapeutic Goods (Medical Devices) Regulations 2002, the conformity assessment test is mandatory for getting clinical acceptance regarding its safety and performance as a premarket assessment [43]. After submitting all the performance evaluation tests, the results have to be submitted to the TGA,

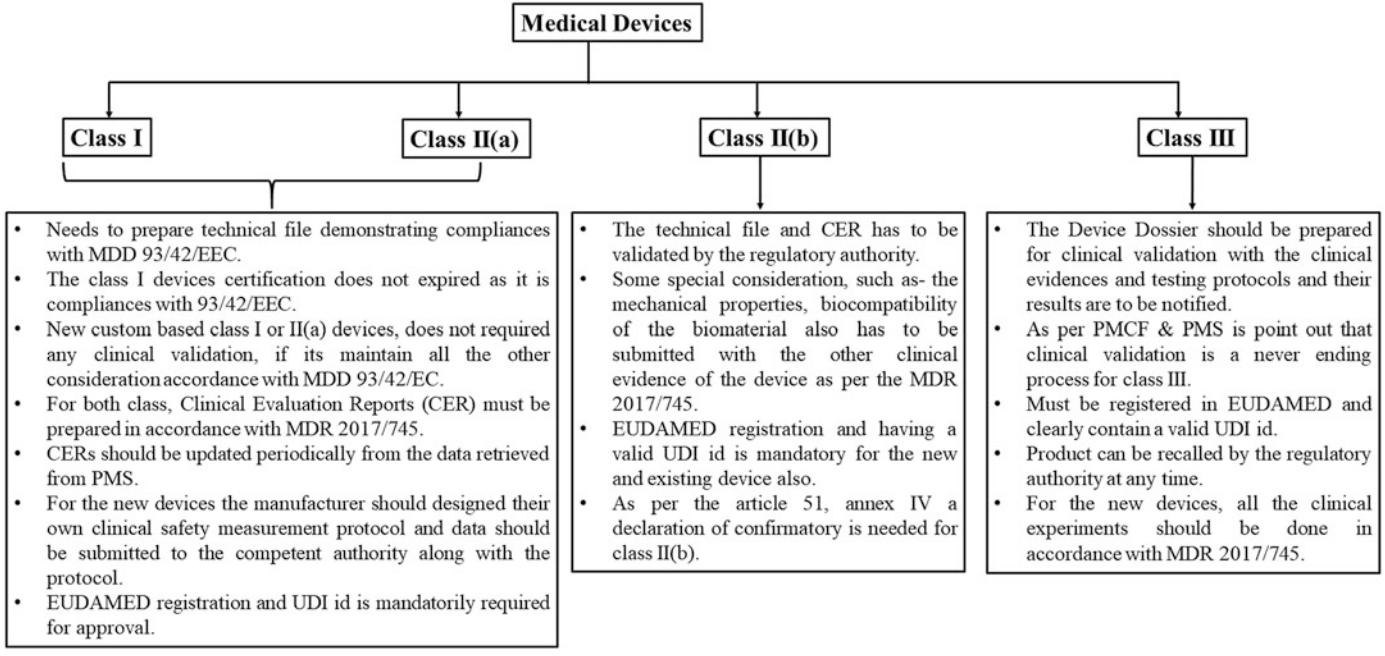


Fig. 11.6 The chart shows the technical documents needed for the clinical assessment in the EU

and then they issued a TGA conformity assessment certificate after cross-checking all the clinical data. The assessment certificate is mandatory for getting permission for the marketing and sales of the device. Usually, TGA follows regulatory compliances same as the EU-MDR. But any manufacturer who wants to market their products in the Australian market must have the TGA approval listing number, and the device must also be included on the Australian Register of Therapeutic Goods (ARTG) unless the device is exempt or excluded from the market. TGA also claims that the clinical evidence data should be updated from time to time by the manufacturer, and TGA can review the data at any time. The regulation also states that CER should be reviewed in each five-year interval relying upon the gadget's oddity and risk, as per MEDDEV 2.7/1 revision 428 (page 12) [44]. Post Marketing Clinical Follow-up (PMCF) is another important criterion that has to be done by the manufacturer to prove strong evidence regarding the safety and efficacy of the device. The degree of conformity assurance required must suit the extent and complexity of using the device, ranging from vendor self-evaluation for low-risk devices to assurance of the manufacturer's quality control framework and analysis by a notified body highest-risk devices of the specification of the individual product [45].

11.8.5 Medical Devices Clinical Validation in China

In China, the National Medical Product Administration (NMPA), previously known as China Food and Drug Administration (CFDA), regulates the regulatory compliance requirements for the Medical Devices and in vitro diagnostic devices. Although China's government decided to make their market more harmonized by adopting a 3-tier risk-based classification system, now some burden is still existing for the Western device manufacturer to get regulatory approval for the Chinese market. This may be because of the complexity of the device registration and the overhauled medical device regulation [46]. According to the NMPA jurisdiction, all the devices must fulfill all the criteria notified in the China Good Clinical Practice requirements (GCP). On November 17, 2017, NMPA published some new regulations regarding accepting foreign clinical evidence data. However, it is also stated that the manufacturer or the Person Responsible for Regulatory Compliance (PRRC) for the Chinese market should be notified to the NMPA for the use of foreign clinical testing data before the application. Generally, NMPA reviews the gap between ethnicity and the clinical confirmatory testing pathway for the foreign clinical evaluation data. While the CFDA testing labs should justify home manufacturer of the China, the clinical validation of the device although self-clinical study reports (CSR) will also be acceptable and should be satisfactory [47]. The degree of clinical evaluation report data varies with the device's risk, for example, the higher risk associated devices like Class III devices will need some additional supplementary device dossier along with the general clinical evidence data [48].

Table 11.3 Some of the internationally acceptable de facto *s*tandards for clinical validation of medical devices

Standards	Description of use
ISO 14971:2007	"It covers aspects including risk management, design control during product development, and verification and validation systems"
ISO 10993-1:2009	"Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process. It is the most widely used standard for assessing medical devices' biocompatibility and materials and provides a framework for determining the appropriate biocompatibility steps for planning a biological evaluation"
IEC 62366–1:2015	"Medical devices—Part 1: Application of usability engineering to medical devices"
IEC 60601–1:2005	"It deals with the basic safety and essential performance requirements of medical electrical equipment and serves to ensure that no single electrical, mechanical, or functional failure shall pose an unacceptable risk to patients and/or operators"
ISO 11135 ISO 11137 ISO 17665	"Requirements for the development, validation, and routine control of sterilization processes for medical devices and other healthcare products. • For ethylene oxide sterilization • For radiation sterilization • For moist heat sterilization"
ISO 14644	"It states all the criteria for cleanroom environments for medical devices"
ASTM F2150–13	"It contains the standard guideline for characterization and testing of biomaterial scaffolds used in tissue-engineered medical devices"
ASTM F2027–16	"It deals with the standard guideline for characterization and testing of raw or starting materials for tissue-engineered devices"

[a]All the above standards must be compared and then complied with the formal mandated standards validated by the target country's regulatory authorities for marketing

Although various countries have their own formulated regulations for medical devices, still some de facto standards are frequently adopted to examine the safety performance and quality of medical devices. Table 11.3 provides a little glimpse about the de facto standards for different devices testing protocols, which are quietly acceptable in various markets.

11.9 Conclusions

The clinical evaluation of medical devices and their validation is one of the uttermost essential regulatory compliance to ensure the three important dimensions of any devices, i.e., quality or performance, safety, and efficacy. Another important aspect of the clinical validation is the quality of the data and its formatting. Recently, IMDRF, under the monitoring of GHTF, is tried to bring all the major regulatory bodies under one roof to facilitate and justify all the necessary criteria or guidelines for clinical validation and its acceptance. Currently, the Summary of Technical Documentation (STED) format is well accepted in different countries, which follows

the IMDRF over clinical data formatting. Some countries like India and Brazil also accept the clinical evaluation data produced outside of the country and may not be asked to be repeated depending on the quality of the data and the credentials of the laboratory where such data has been generated. So, it seems that all are trying to make the clinical data evaluation pathways more stringent and more effective over the device classes. The execution of EUDAMED or UDI suggests that the effective implementation of such regulatory submission can make a leap forward to a stringent clinical validation process and increase customer compliance. Thus, the requirement of clinical validation is needed for regulatory approval and needed for the user's satisfaction throughout the device lifetime.

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