WHITE PAPER

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MEDICAL DEVICE

Medical Device Development:
Pathways to Clearance or Approval in the U.S. and the EU

ABSTRACT

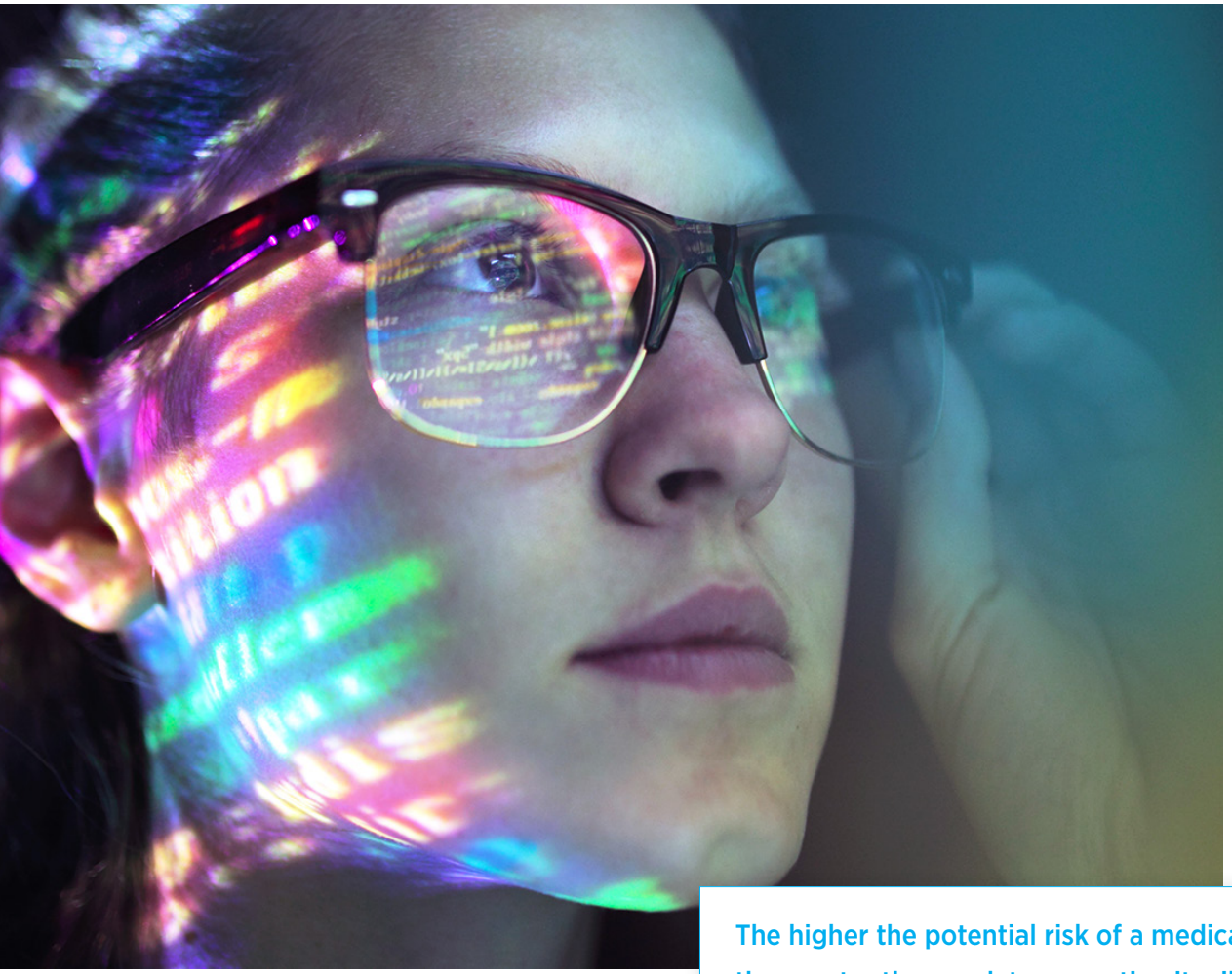
Although the development processes for medical devices and drugs follow the same basic steps, there are key differences between the regulations, approval pathways, and clinical investigations required for each, both in the United States and in the European Union.

Understanding where the development pathways for devices and drugs diverge is a critical first step in ensuring proper planning throughout the medical device development process.

Introduction

Although medical device development is similar in many ways to drug development, devices are subject to different regulatory requirements and approval pathways than drugs. There are also key differences in the rules for the clinical investigations needed to support marketing approval, in part due to the durable nature of devices, which may be implanted in patients' bodies for extended periods. Understanding where the development pathways for devices and drugs diverge is a critical first step in ensuring proper planning throughout the medical device development process, from discovery to post-market surveillance.

In this white paper, we explore the development process, regulatory landscape, and pathways to approval for medical devices to help sponsors optimize the likelihood of commercial success.



Key distinctions between medical devices and drugs

Fundamental differences between medical devices and drugs contribute to differences in the development of – and regulatory process for – medical devices. While drugs are designed to act therapeutically by pharmacological, immunological, or metabolic means, devices can act in multiple ways on the human body, depending on their purpose. A device may be therapeutic or diagnostic in nature, or it may be designed for another medical purpose. A medical device may have multiple components – including hardware, software, and/or medicinal constituents – that work in concert to achieve its intended purpose. It may require multiple clinicians to work together to ensure it is administered, applied, or implanted properly.

Unlike drugs, most of which have a similar mode of action and are usually metabolized by the body, medical devices vary significantly in their complexity, mode of action, and purpose, and they may even remain with or be implanted in a patient's body on a permanent basis. This can result in additional risks, such as device malfunctions or long-term adverse effects. Due to this variability and complexity, medical devices are classified according to their inherent risk to patients and users. The higher the potential risk of a medical device is, the greater the regulatory scrutiny it will face. This risk classification concept is another distinction between medical devices and drugs, and it can have a significant impact on the device development process and the data required for market approval.

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Regulatory landscape in the U.S. and EU

Figures 1a and 1b outline the current regulations and guidance focusing on clinical investigations and good clinical practice (GCP) for medical device trials in the U.S. and the EU. Sponsors should note that there are other standards and guidance documents – such as those for good manufacturing practices, risk management (ISO 14971[1]), quality management systems (ISO 9001[2]; ISO 13485[3]), and preclinical development (ISO 10993[4]) – that are not addressed in this white paper. Also, in vitro diagnostic medical devices fall outside the scope of this paper. ISO 14155:2020 addresses good clinical practice for the design, conduct, recording, and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.[5] While ISO 14155:2020 is not part of the official U.S. Food and Drug Administration (FDA) regulatory requirements for medical devices, the FDA recognizes the principles it sets forth.

US	
ISO 14155:2020[5]	Addresses good clinical practices in investigation of medical devices for human subjects. It is not required to be followed in the U.S., but the FDA recognizes this ISO document except the section concerning the protection of human subjects, which is addressed in 21 CFR Part 50
21 CFR[6] Part 11 – Electronic Records	Sets out criteria under which the FDA considers electronic records, electronic signatures, etc., to be equivalent to paper records and handwritten signatures
21 CFR Part 50 – Protection of Human Subjects	Addresses protection of human subjects with regard to clinical investigations
21 CFR Part 54 – Financial Disclosure by Clinical Investigators	Describes the process for clinical studies to avoid bias resulting from potential financial interests of investigators
21 CFR Part 56 – Institutional Review Boards	Contains general standards for the composition, operation, and responsibility of institutional review boards when reviewing clinical investigations
21 CFR Part 812 – Investigational Device Exemptions	Provides procedures for the conduct of medical device clinical investigations
21 CFR Part 814 – Premarket Approval of Medical Devices	Specifies the procedure for premarket approval of any Class III medical device for human use, unless exempted

Figure 1a. GCP-related medical device regulations and guidance

Figure 1b.

EU	
ISO 14155:2020	Must be followed in the EU for all clinical investigations involving medical devices intended for human use
Medical Device Regulation 2017/745/EU (MDR)[7]	Replaces the former Medical Device Directive (MDD), Directive 93/42/EEC, and Active Implantable Medical Device Directive (AIMDD); date of application is May 26, 2021
Relevant EU Guidance Documents: • Medical Devices documents (MEDDEVs)[8] • Medical Device Coordination Group documents (MDCGs)[9]	Provided by the EU Commission to assist stakeholders in implementing the medical device regulations. In this transition time, both types of guidance documents (MEDDEVs and MDCGs) can be applicable, depending on the topic. In the future, all MEDDEVs will be replaced by MDCGs
Relevant clinical MDCGs: • MDCG 2020-10/1: Guidance on safety reporting in clinical investigation • MDCG 2020-8: Guidance on post-market clinical follow-up (PMCF) evaluation report template • MDCG 2020-7: Guidance on PMCF plan template • MDCG 2020-6: Guidance on clinical evidence for legacy devices • MDCG 2020-5: Guidance on clinical evaluation – Equivalence • MDCG 2019: Summary of safety and clinical performance	Published by the EU Medical Devices Coordination Group to assist with the new Medical Device Regulation (MDR) and explain how the regulation should be implemented
Sampling of relevant clinical MEDDEVs: • 2.7/2 Rev. 2 Guidelines for Competent Authorities for Making a Validation/ Assessment of a Clinical Investigation Under Directives 90/385/EEC and 93/42/EC • 2.7/4 Guidelines on Clinical Investigations: A Guide for Manufacturers and Notified Bodies • 2.12/1 Guidelines on a Medical Devices Vigilance System • 2.12/2 Rev. 2 Post-market clinical follow-up studies	Released to close interpretation gaps in the former MDD/AIMDD and to promote a common approach in conformity assessment

While ISO 14155:2020 is not part of the official U.S. Food and Drug Administration (FDA) regulatory requirements for medical devices, the FDA recognizes the principles it sets forth.

Recent updates in the U.S.

The 21st Century Cures Act, enacted in December 2016, includes a number of provisions that affect medical device sponsors. These are outlined in Figure 2.

Provision / Summary
Breakthrough Device Designation (Section 3051) Establishes an expedited review program for devices intended to treat or diagnose life-threatening or irreversibly debilitating diseases or conditions. This is similar to the existing breakthrough therapy designation program for drugs and biologics and applies to 510(k), De Novo petitions, and premarket approval applications (PMAs)
Humanitarian Device Exemption (Section 3052) Creates a new regulatory pathway for devices intended to address rare diseases or conditions that affect up to 8,000 people annually
Recognition of Standards (Section 3053) Requires the FDA to determine and publicly disclose within 60 days of a submitted request whether a nationally or internationally recognized standard will be officially adopted
510(k) Exemptions for Class I/II Devices (Section 3054) Requires the FDA to publish a list of Class I and II devices that no longer require 510(k) clearance every five years
Institutional Review Board Flexibility (Section 3056) Removes the requirement that local IRBs approve device trials
Clarifying Medical Software Regulation (Section 3060) Amends the definition of devices regulated by the agency to remove software that uses “big data” to provide clinical decision support to health care professionals

Figure 2. 21st Century Cures Act device provisions[10]

To reinforce a high standard in the development of medical devices, the European Union has created regulations that apply uniformly to all EU countries as soon as they enter into force Regulations 2017/745 and 2017/746.

Recent EU updates

In response to safety concerns associated with some medical devices, the European Commission has published revisions of its former directives. Problems were also observed with the scope of interpretation of the directives. To reinforce a high standard in the development of medical devices, the European Union has created the following regulations that apply uniformly to all EU countries as soon as they enter into force:

- Regulation (EU) 2017/745 on medical devices (MDR), latest corrigendum Dec. 27, 2019
- Regulation (EU) 2017/746 on in vitro diagnostic medical devices (IVDR), latest corrigendum Dec. 27, 2019[11]

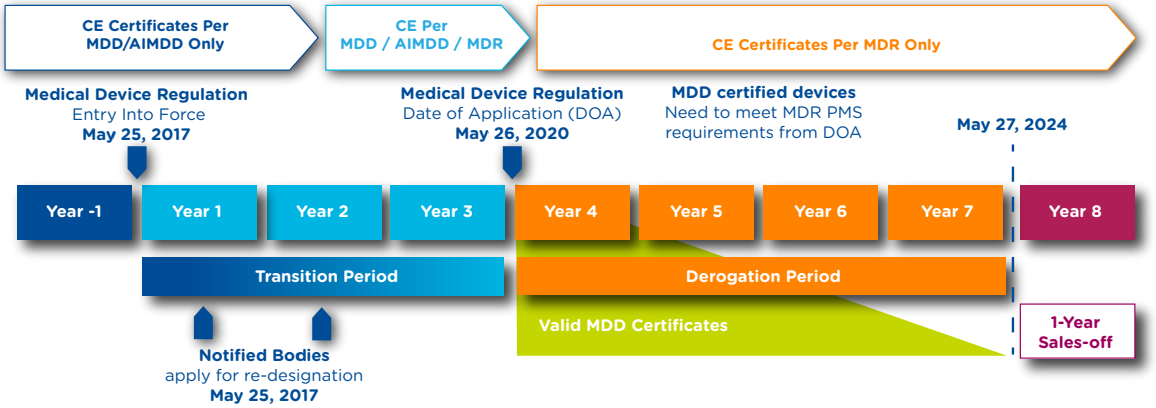
The two new regulations replace the previous three directives (AIMDD – Active Implantable Medical Devices Directive, MDD – Medical Devices Directive, and IVDMD – In Vitro Diagnostic Medical Devices) and were adopted in April 2017. On May 25, 2017, the regulations took effect in all EU member states.

A three-year transition period was set out with an original application date of May 26, 2020, for the MDR, which covers all devices previously addressed under the MDD and AIMDD. A five-year transition period was set for the IVDR (May 2022). In light of the coronavirus crisis, the EU Council and Parliament extended the application date by one year to reduce the pressure on national authorities, notified bodies, and manufacturers.

During the transition period, all CE certificates issued before the MDR came into force will remain valid for the period stated on the certificate. The last CE certificate was issued under the MDD on May 24, 2017, and will expire on May 24, 2022. From that date onward, all medical devices must be in compliance with the MDR and must follow the new conformity assessment to be marketed in the EU. Any devices with only old MDD/AIMDD certificates will be prohibited.

Figure 3: Transition timeline

Transition Timeline from Medical Device Directive to Regulation



The new regulations were created to establish a robust, transparent, predictable, and sustainable regulatory framework that will ensure a consistently high level of health and safety protection for EU citizens while supporting innovation of medical devices.

The MDR is a 175-page document with 123 articles and 17 annexes. In comparison, the MDD had 43 pages, 23 articles, and 12 annexes. The new MDR has a broader scope compared with its predecessor, incorporating all existing requirements in addition to new ones.

Medical device sponsors should be aware of a few key changes resulting from the MDR:

- **Greater emphasis on the life-cycle approach with regard to safety, including post-market surveillance and vigilance**
- **Stricter requirements for notified bodies (NBs) and their designation process** NBs are subject to higher accreditation standards and increased control by national competent authorities. NBs must become recertified to grant CE certificates under the MDR/IVDR. In addition, NBs are required to perform unannounced manufacturer and supplier audits.
- **Reclassification of certain devices with more products now regulated as medical devices, for example, devices for cleaning, sterilizing, or disinfecting other devices** There are now 22 classification rules in Annex VIII, compared to 18 rules under the former MDD.
- **Stricter requirements for the level of clinical evidence required to support medical device assessment** Class III devices and implants, with few exceptions, require clinical investigations. Equivalence demonstrations are no longer accepted as the only method to demonstrate compliance. The MDR also requires a clinical evaluation consultation by an independent expert panel.
- **The requirement to appoint and make available a person responsible for regulatory compliance**
- **The obligation to fulfill Annex I with regard to the general requirements, design, and labeling of devices**
- **A new classification system and requirements for IVDs** In vitro diagnostics (IVDs) are classified from Class A (low risk) to Class D (highest risk), and NBs must participate in the evaluation of Class B to Class D IVDs.
- **Regulation of companion diagnostics by competent authorities for the first time under the IVDR**

The EU Commission provided high-level guidance on how to implement the MDR, defining steps for manufacturers from pre-assessment via gap analysis to resulting actions from the analysis to implementation.[12]

Device development process

Drugs achieve their action in the body by pharmacological, immunological, or metabolic means to either promote healing or prevent a disease from progressing, but a medical device can act in multiple ways on the body, depending on its purpose. Medical devices range from simple wooden tongue depressors to complex laser surgical devices and cardiac pacemakers.

In 2013, the FDA issued the guidance document Design Considerations for Pivotal Clinical Investigations for Medical Devices, which highlights special regulatory considerations that differentiate medical device trials from pharmaceutical drug trials. According to this document, the following factors need to be taken into account when planning a clinical investigation involving devices:[13]

Device complexity. An understanding of the scientific principles underlying a device's function and mechanism of action may be

Equivalence demonstrations are no longer accepted as the only method to demonstrate compliance. The MDR also requires a clinical evaluation consultation by an independent expert panel.

relevant to clinical investigators and patients in assessing the performance and adequacy of the proposed study design.

User skill level and training. Some devices require considerable skill and training to be used in a safe, effective manner. In some cases, multiple skill sets or personnel are required for the appropriate use of the device. The training provided to study investigators and staff should guide the training that will be provided to users when the device is marketed. If no training will be provided for the marketed device, study personnel should not be trained in the use of the device either. This will ensure that the study reflects intended use conditions.

Learning curve. The use of novel devices may require a learning curve, so it may take time for users to master the necessary steps prior to using a device in a clinical study. For some devices, the learning curve can be assessed in the exploratory stage. Devices with steep learning curves may not be appropriate or safe for use in some settings, such as homes.

Human factor considerations. Human factors play a crucial role in the development of medical devices. At any point in the development process, the study of the human factors associated with the use of the device may necessitate changes to the device's design or its instructions for use in order to make the device safer, more effective, or easier to use.

Medical device development involves the following steps:

1. **Concept and design phase.** Once a concept for a device has been developed, it must be evaluated in terms of indication, targeted population, and the applicable health care market. Device materials and modes of action are confirmed during the design phase.

2. **Regulatory strategy plan.** The proposed claim and indication are selected. Based on the risk classification of the device, the regulatory submission strategy and required technical documentation are determined. Sponsors should note that the classification of a device may differ in the U.S. and the EU (see Figure 4 and Figure 5).

3. **Preclinical phase**. During this step, researchers build a prototype of the device that is not for human use. This prototype is tested in a controlled laboratory setting or in animal models for material characterization, stability, and biocompatibility. It is then refined based on the data gathered to reduce the potential risk of harm in people. Methods, such as sterilization and packaging, are also validated.

   All preclinical data, literature data for comparator devices, and results of the risk analysis are entered into the clinical evaluation report. Risks that cannot be fully assessed preclinically are evaluated against the anticipated benefits in clinical studies for high-risk devices. Upscaling device manufacturing from prototype via design freeze-up to a sufficient number of devices for the clinical phase is also necessary.

4. **Clinical phase.** The device is tested in people to ensure it is safe and performs as intended. Sponsors should note that the stages and sizes of medical device studies are different from drug studies (see Figure 6). Premarket clinical investigations usually undergo review by the Competent Authority and Ethics Committee in the EU, whereas in the U.S., such studies are reviewed by the FDA and assessed by institutional review boards to ensure the protection of human subjects. In medical device trials, safety reporting also looks at serious events caused by the device or the implant procedure. These are called serious adverse device effects, and such events must be carefully assessed in terms of relatedness and expectedness and may also need to be reported to the health authorities.

   In the EU, device deficiencies must be collected and should be reported if they could have led to a serious adverse device effect under less fortunate circumstances or if they resulted

in a serious adverse event that is related to the device or the procedure. All results of preclinical and clinical studies must be summarized in the clinical evaluation plan. The overarching goal of the preclinical and clinical phases is to have sufficient clinical evidence available to show that a device is safe and achieves its intended clinical benefits. The EU Commission's MDCG Guidance on Clinical Evaluation – Equivalence provides more insight on other potential sources of clinical data.[14]

5. **Regulatory review.** All collected device data, from manufacturing processes data to clinical data, is gathered in the technical documentation and reviewed by the regulatory body. In the EU, this is the notified body for high-risk devices. The degree of NB involvement differs based on device class. The NB may also perform a manufacturer inspection during the review process. If the NB assesses the device as safe and performing as intended, the manufacturer receives the EC certificate of conformity. If the device is considered low-risk, the manufacturer performs a self-certification. Finally, the manufacturer prepares the declaration of conformity and registers the device to put it on the market after the CE mark has been affixed.

6. **Post-market surveillance (PMS).** Manufacturers must have a PMS system in place per MDR Article 32. PMS is a collection of processes and activities used to monitor the performance of a medical device in a real-world setting and generate information regarding the use of the device to help identify any problems after the device is put on the market. Post-market clinical follow-up studies or registries are usually part of the proactive PMS activities to actively gain insight into device performance and safety when the device is used according to instructions. The manufacturer must report device-related safety events, called incidents, to the regulatory authorities.

Investigational device exemptions vs. investigational new drug applications

There are several similarities between the requirements for investigational device exemptions (IDEs) and investigational new drug (IND) applications.

A notable difference is that IDEs require hands-on device training for investigator site staff, because the efficacy and safety of the device may be highly dependent on the technique applied. In addition, not all adverse events are reportable under an IDE, due to the local effect of the device. The responsibility for reporting adverse events related to devices is shared between the users and the manufacturers. A detailed explanation of these responsibilities is found within the FDA guidance under Mandatory Reporting Requirements.[15]

Figure 4. Requirements for IDEs and INDs

	IDE (21 CFR Part 812)	IND (21 CFR Part 312)
Requires that an appropriate submission be made to the FDA prior to initiating the study	√	√
Specifies labeling requirements	√	√
Addresses waivers	√	√
Describes investigator responsibilities	√	√
Requires selection of qualified investigators	√	√
Requires study monitoring	√	√
Requires IRB approval prior to initiating the study	√	√

Stages of medical device clinical investigations

If a clinical investigation is required, medical devices may undergo three general stages of clinical study that may be highly dependent on each other. Performing a rigorous evaluation in one stage can make the next stage more straightforward.

Classification of medical devices

Medical device classification is based on the risk posed by the particular device and is the determining factor for the required development process and approval pathway.

In the U.S., classification is determined by the FDA. Searching the FDA Product Classification database can reveal the classification of an existing comparator device or indicate whether any exemptions may exist. Figure 6 provides more information about classification.

In the EU, there is a two-step process for device classification:

1. **Determine the applicable regulation.** The manufacturer is responsible for determining which regulation is applicable to the device: the Medical Devices Regulation or the In Vitro Diagnostics Regulation. Most devices fall under the MDR.
2. **Determine the class.** Each regulation has its own rules-based classification scheme. Unlike the U.S., which relies on predicate devices when determining approval pathways, the EU system does not distinguish between new and existing devices.

Device Studies*	Drug Studies
Premarket Phase	
Pilot Stage: Exploratory: Small study (10-30 patients with the condition) to determine preliminary safety and performance Type of study: ▪ First-in-human study ▪ Feasibility study	**Phase 1:** Small study (20-100 healthy volunteers or people with condition) to determine preliminary safety and dosage
Pivotal: Larger study (150-300 patients with the condition) to determine efficacy and adverse effects	**Phase 2:** Larger study (up to several hundred people with the condition) to establish clinical proof of concept, preliminary efficacy, and characterization of adverse effects
	Phase 3: **(sometimes known as a pivotal or confirmatory study)** Even larger study (up to thousands of people with the condition) to determine efficacy and monitor adverse effects
Post-Market Phase	
Studies conducted using marketed devices according to the intended use/population. They can be: ▪ *Investigational:* Add additional assessments outside the standard-of-care use; also known as post-market clinical follow-up (PMCF) studies. ▪ *Observational:* • *Intended to answer specific questions (PMCF study)* • *Data collection on routine use of the device (registry)*	**Phase 4:** Post-market study to collect long-term data

Figure 5. Stages of clinical development: Device vs. drug
*Note: Not all devices must go through all stages

The MDR lays out its classification rules in Annex VIII. In general, classification rules are governed by the intended purpose of the device, and this annex provides specific definitions for device classification, such as duration of use and what qualifies as an invasive or active device. In general, the classification depends on a series of factors, including:

- How long the device will be applied
  - Transient: < 60 minutes
  - Short term: ≥ 60 minutes to ≤ 30 days
  - Long term: > 30 days
- Degree of invasiveness
  - Is the device applied via a natural body orifice or surgery?
- Whether it is an active device
  - Does the device depend on a source of energy to operate?
- Location of the device
  - Is it applied to the skin, or does it interact with parts of the cardiovascular or central nervous system?

Device classification is a very complex topic, as parameters other than the intended use can affect the classification, such as when devices contain software or are combined with other components or even drugs. This may lead to an even more complex regulatory situation requiring adherence to regulations for drugs and medical devices.

In general, the EU divides medical devices into four risk classes, whereas in the U.S., there are three classes and risk per se is also evaluated. However, the general concept is the same: The greater the inherent risk of the device to cause potential harm to the patient or user, the higher the risk class.

U.S.			
	Class I	**Class II**	**Class III**
Description	Low risk	Medium risk	Supports or sustains life, is implanted in the body, or has the potential for unreasonable risk of illness or injury
Requirements	General controls ▪ Good manufacturing practices ▪ Standards and reporting adverse events ▪ Registration ▪ General recordkeeping requirements	General controls with special controls: ▪ Labeling requirements ▪ Device-specific mandatory performance standards ▪ Device-specific testing requirements	General controls and premarket approval
Examples	▪ Oxygen masks ▪ Surgical gloves	▪ Knee prosthetics ▪ Single-use scalpels	▪ Pacemakers ▪ Breast implants

Figure 6. Medical device classification in the U.S.[16]

EU				
	Class I	**Class IIa**	**Class IIb**	**Class III**
Description	Low risk	Low-medium risk	Medium-high risk	High risk
Requirements	Usually, a self-assessment by the manufacturer; however, a notified body could be involved if the device is used as a measuring tool or is a reusable surgical instrument	▪ Technical file required ▪ NB will review quality management system (QMS) ▪ NB will verify data of representative device of a category	▪ Technical file required ▪ NB will review QMS ▪ NB will verify data of representative device of generic device group	▪ Technical file required ▪ QMS needs to be certified ▪ NB review ▪ Expert panel review
Examples	▪ Blood bags ▪ Wound dressings (e.g., wound strips)	▪ Hearing aids ▪ Dental fillings	▪ Ventilators ▪ Intensive care monitoring equipment	▪ Drug-eluting stents ▪ Prosthetic heart valves

Figure 7. Medical device classification in the EU[17]

> **The pathway to clearance for a medical device in the U.S. depends on its risk classification and the level of control necessary to provide reasonable assurance of its safety and effectiveness.**

Applying standards to device trials

Standards are formal documents that establish uniform methods or processes regarding how products should be manufactured or developed and how clinical investigations of those products should be conducted.

The International Organization for Standardization recently published ISO 14155:2020, which defines principles of good clinical practice to protect the rights, safety, and well-being of human subjects in clinical investigations of medical devices. This standard ensures that such investigations are conducted scientifically and that the study results are credible. It defines the responsibilities of the sponsor, the principal investigator, and to a certain degree, the ethics committees. Highlights of the newly published standard are:

- Addition of a summary section for the GCP principles
- More emphasis on risk-based monitoring
- Additional guidance on clinical quality management
- Risk-based approach
- Additional guidance for ethics committees

Data from prospective clinical trials is typically needed when:

- Developing a Class III or implantable device
- Components, features, and/or methods of action are previously unknown
- An existing device is modified in such a way that the clinical performance and/or safety may be significantly affected
- A device uses new materials with which there is no prior clinical experience
- An established device is proposed for a new indication

To maximize the likelihood of acceptance of the clinical data generated at every stage of development, medical device trials must be designed to meet ISO 14155 guidelines. Some specific requirements, such as device accountability, can be omitted only in post-market, non-interventional studies as detailed in Annex J of the ISO 14155 revision.

Approval pathways

In the U.S.

In the U.S., the responsible regulatory authority for medical devices is the FDA's Center for Devices and Radiological Health. The pathway to clearance for a medical device in the U.S. depends on its risk classification and the level of control necessary to provide reasonable assurance of its safety and effectiveness.

Device pathways to market in the U.S. include:

- Exemption from premarket submission: Applies to most Class I devices
- Premarket Notification [510(k)]: Applies to some Class I and most Class II devices where a predicate is already on the market
- Premarket Approval: Applies to most Class III devices
- De Novo (Evaluation of Automatic Class III Designation): Applies to new devices without a valid predicate that would otherwise be classified as Class II or III
- Humanitarian Device Exemption: Applies to Class III devices intended to benefit patients with rare diseases or conditions

Of note, the FDA has issued draft guidance on the use of real-world evidence to support regulatory decision-making for medical devices.[18]

In the EU

In the EU, devices are put on the market following risk-based conformity assessments that typically involve a notified body, although this depends on the risk classification. Notified bodies are independent commercial organizations that are designated, monitored, and audited by the relevant EU member states via their national competent authorities. Before a device can be marketed in Europe, a notified body must assess whether or not the product conforms to all requirements.

Due to the change in regulation, notified bodies must undergo an assessment by the EU to be accredited under the new MDR and to assess products according to the new regulation. Currently, only 14 NBs are accredited under the MDR throughout Europe, imposing additional hurdles for manufacturers seeking an NB with the capacity to assess their products. However, in general, manufacturers are free to choose any NB that has been legally designated to carry out the conformity assessment procedure.

The Medical Device Regulation defines the conformity assessments required for medical devices based on their classification, and the pathway to market is the CE marking.

Conclusion

Medical device and pharmaceutical drug trials share the common goal of safeguarding patients while bringing safe and effective products to market as quickly and efficiently as possible. However, there are key differences when it comes to the development of medical devices, and sponsors must develop a thorough understanding of the regulatory landscape and approval pathways to bring their devices to market. The regulatory requirements related to device development are ever-evolving, and significant changes are ongoing, so it is critical for sponsors to stay informed and up to date.

Sponsor responsibilities for running clinical investigations have increased, as have the requirements to generate sufficient clinical data. Areas such as informed consent, risk assessment, monitoring, document control, and electronic data management have become better defined, with more stringent requirements. The new ISO 14155 revision continues this trend and further increases the requirements for clinical investigations. An experienced contract research organization can help sponsors improve data quality and navigate the device development process more smoothly during the clinical stage and beyond. It's important to work with an organization that has device experience, can differentiate between the necessities and particularities of a drug trial versus those applicable to a clinical investigation with medical devices, and has the proven capability to build quality by design into a clinical trial program.

	U.S.	EU
Step One	Determine classification of the device	Determine device classification, either according to MDR or IVDR
Step Two	Choose the correct premarket submission route: ▪ 510(k) (premarket notification) ▪ PMA (premarket approval) ▪ De Novo (Evaluation of Automatic Class III Designation) ▪ HDE (humanitarian device exemption)	▪ Prepare technical documentation ▪ Implement QMS according to ISO 13485
Step Three	Prepare a premarket submission to the FDA	For higher-risk devices: Have the technical documentation and QMS audited by a notified body
Step Four	Submit the premarket submission and interact with the FDA during the review	Obtain CE marking and ISO 13485 certificates (if appropriate) from the notified body
Step Five	Complete the establishment registration and device listing	Prepare declaration of conformity stating that the device complies with the regulation

Figure 8. Steps involved in obtaining market approval in the U.S. and the EU

References

1. International Organization for Standardization. (2019). Medical devices – Application of risk management to medical devices (14971).
2. International Organization for Standardization. (2015). Quality management systems – Requirements (9001).
3. International Organization for Standardization. (2016). Medical devices – Quality management systems – Requirements for regulatory purposes (13485).
4. International Organization for Standardization. (2018). Biological evaluation of medical devices (10993-1).
5. International Organization for Standardization. (2020). Clinical investigation of medical devices for human subjects – Good clinical practice (14155).
6. Code of Federal Regulations - Title 21. Available at https://www.ecfr.gov/cgi-bin/text-idx?SID=b100e5a52e79f34452d505b51c4e6461&mc=true&tpl=/ecfrbrowse/Title21/21tab_02.tpl.
7. 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. European Parliament, Council of the European Union. https://eur-lex.europa.eu/eli/reg/2017/745/2020-04-24.
8. European Commission. Guidance MEDDEVs. Available at https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_guidance_meddevs.pdf.
9. European Commission. Guidance – MDCG endorsed documents. Available at https://ec.europa.eu/health/md_sector/new_regulations/guidance_en.
10. Congress.gov. H.R.6 – 21st Century Cures Act, 114th Congress (2015-2016). Available at https://www.congress.gov/bill/114th-congress/house-bill/6.
11. Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU. European Parliament, Council of the European Union. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02017R0746-20170505.
12. European Commission. Implementation Model for Medical Devices Regulation – Step by Step Guide. Available at https://ec.europa.eu/docsroom/documents/33661.
13. U.S. Food and Drug Administration. Design Considerations for Pivotal Clinical Investigations for Medical Devices – Guidance for Industry, Clinical Investigators, Institutional Review Boards and FDA Staff. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/design-considerations-pivotal-clinical-investigations-medical-devices.
14. European Commission. MDCG 2020-5 Clinical Evaluation – Equivalence: A guide for manufacturers and notified bodies, April 2020. Available at https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020_5_guidance_clinical_evaluation_equivalence_en.pdf.
15. U.S. Food and Drug Administration. Mandatory Reporting Requirements: Manufacturers, Importers and Device User Facilities. Available at https://www.fda.gov/medical-devices/postmarket-requirements-devices/mandatory-reporting-requirements-manufacturers-importers-and-device-user-facilities.
16. U.S. Food and Drug Administration. Step 1: Device Discovery and Concept. Available at http://www.fda.gov/ForPatients/Approvals/Devices/ucm405378.htm.
17. European Commission. Medical Devices: Guidance document – Classification of medical devices, June 2010. Available at https://ec.europa.eu/docsroom/documents/10337/attachments/1/translations/en/renditions/pdf.
18. U.S. Food and Drug Administration. Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices: Guidance for Industry and Food Administration Staff, August 2017. Available at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM513027.

Nach Davé | RPh, MS, Vice President, Development Strategy

Nach Davé provides strategic and commercial input for Premier Research business activities. He brings more than 20 years of experience in the pharmaceutical and contract research industries to the position. He has served as the Vice President of Regulatory at Premier and has been in leadership positions at both CROs and sponsor companies. Mr. Davé previously led clinical and regulatory affairs at Maxx Orthopedics, a developer of orthopedic medical devices, and has held roles in clinical operations, business development, strategic consulting, and medical affairs at companies such as Merck, Bristol-Myers Squibb, Aventis Pharmaceuticals, and Mitsubishi Pharma America. In his current role, Mr. Davé brings innovative solutions to grow the Premier Research footprint in the areas of medical device development, real-world evidence, and government relations. He is keen to explore how innovative technology like AI, ML, and other developments can best support the growth of Premier's business. Mr. Davé holds a master's degree in drug regulatory affairs from Long Island University and a bachelor's degree in pharmacy from the University of Sciences-Philadelphia. He is a registered pharmacist.

Janet Kube | Senior Director, Program Delivery, Medical Device & Diagnostics

Janet Kube is responsible for ensuring operational excellence in collaboration with leadership and in support of the overall Medical Device & Diagnostics group, including collaborating with global resourcing on assignments as well as activity and metrics reporting, overseeing assigned project managers and directors, and empowering them to lead and direct global cross-functional teams and manage client expectations to achieve client satisfaction. In her role, Mrs. Kube also operates at a strategic support level for complex, critical, therapeutically aligned programs through key stakeholder engagement and cross-functional management.

With more than 20 years of experience in clinical drug development as well as medical device licensing exclusively in the CRO environment, she has taken on the responsibility of operational delivery on various trials and clients, with a focus on the cardiovascular as well as the orthopedic and pediatric fields. Before joining the drug development industry, Mrs. Kube worked as a Registered Pediatric Nurse in several departments of a pediatric hospital, including the neuro-pediatric and oncology ward.

About Premier Research

Premier Research, a clinical research company, is dedicated to helping biotech, specialty pharma, and device innovators transform life-changing ideas and breakthrough science into new medical treatments.

As a global company, Premier specializes in the use of innovative technologies for smart study design and trial management to deliver clean, conclusive data to sponsors.

Whether it's developing product lifecycle strategies, reducing clinical development cycle times, securing access to patients, navigating global regulations, maximizing the impact of limited rare disease data, or providing expertise in specific therapeutic areas, Premier is committed to helping its customers answer the unmet needs of patients across a broad range of medical conditions.

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