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

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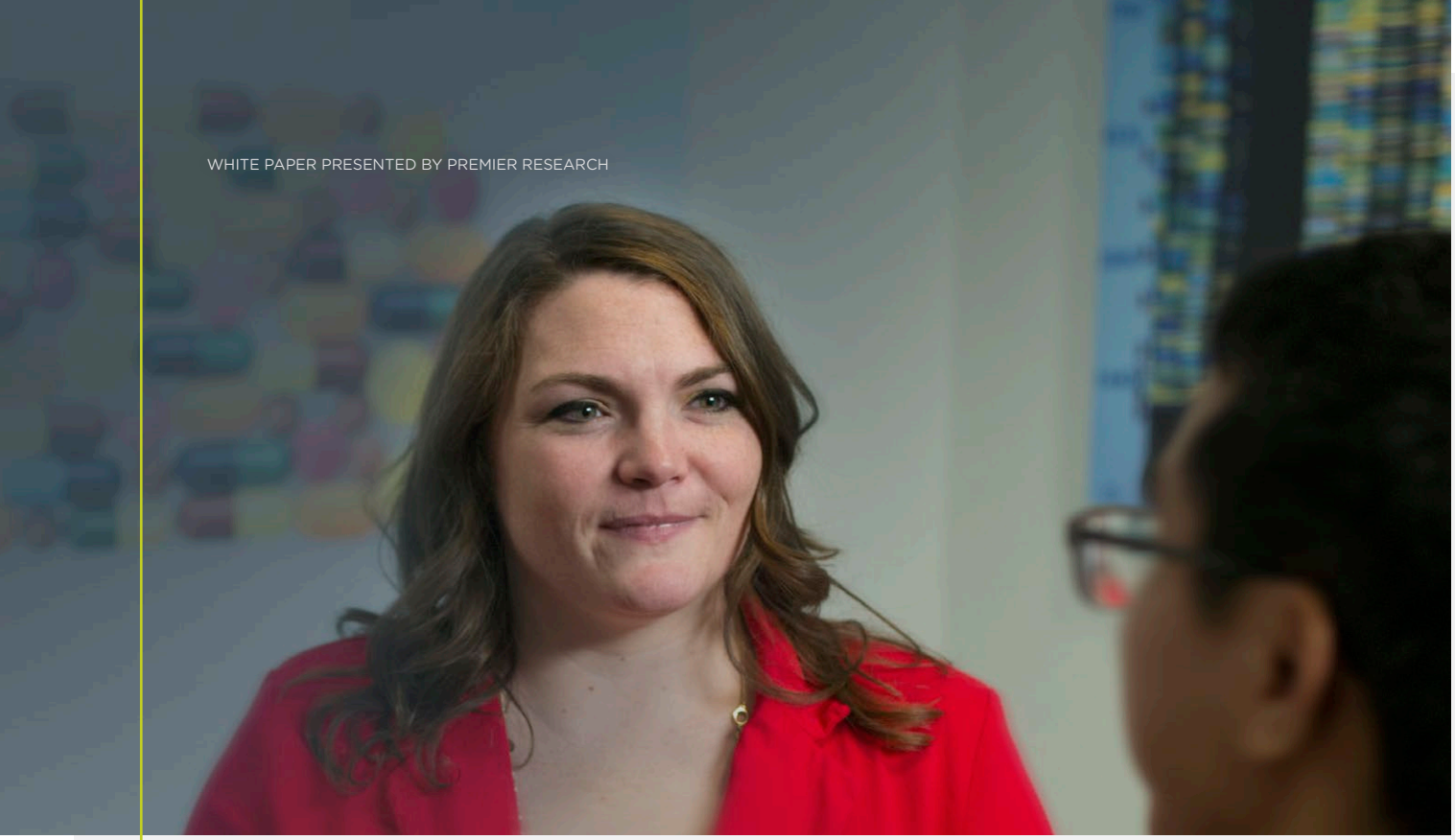
ABSTRACT

While the development processes for devices and drugs follow the same basic steps, there are key differences in the regulations, approval pathways, and clinical investigations required for medical devices, both in the U.S. and in the EU.

MEDICAL DEVICE



Introduction

Although medical device development has core similarities to drug development, devices are subject to different regulatory requirements and approval pathways. There are also key differences in the clinical investigations needed to support marketing approval, in part due to the durable nature of devices, which may be implanted in the patient's body for an extended period. Understanding where the development pathways for devices and drugs diverge is a critical first step for ensuring proper planning along the medical device development continuum, from discovery to post-marketing surveillance.

In this white paper, we explore the development process, regulatory landscape, and pathways to approval for medical devices with the goal of helping sponsors to design clinical development strategies that optimize the likelihood of commercial success.

Key distinctions between devices and drugs

Fundamental differences between devices and drugs contribute to differences in the development of – and regulatory process for – medical devices. While drugs are generally designed to be therapeutic, devices may be therapeutic, diagnostic, or designed for another use. A device may have multiple components – hardware, software, and/or medicinal constituents – which work in concert to achieve its intended use, and it may require multiple clinicians to work together to ensure that it is administrated, applied, or implanted properly. Unlike drugs, which have a half-life and are metabolized by the body, devices may remain with or be implanted in a patient's body. This can result in device malfunctions, in addition to possible long-term adverse effects. Devices are also distinguished from drugs by their classification according to risk. This classification can have a significant impact on the device development process and the data required for market approval.

Understanding where the development pathways for devices and drugs diverge is a critical first step for ensuring proper planning along the medical device development continuum, from discovery to post-marketing surveillance.

Regulatory landscape in the U.S. and EU

The table below outlines the current regulations and guidance around medical device trials in the U.S. and the EU which focus on good clinical practice. Sponsors should keep in mind that there are also regulatory standards for Good Manufacturing Practices (GMPs), risk management (ISO 14971), quality management systems (ISO 9001), and in vitro diagnostic medical devices which fall outside the scope of this paper.

Figure 1. GCP-Related Medical Device Regulation

U.S.	EU
21 CFR Part 11 – Electronic Records[1]	**Relevant Medical Device Directives, including:** › Council Directive 93/42/EEC: Medical Devices Directive (MDD) › Council Directive 90/385/EEC: Active Implantable Medical Devices Directive (AIMDD) › Council Directive 98/79/EC: In Vitro Diagnostics Directive (IVDD)
21 CFR Part 50 – Protection of Human Subjects[2] Part 54 – Financial Disclosure by Clinical Investigators[3] Part 56 – Institutional Review Boards[4]	**Relevant MEDDEVs, including but not limited to:**[5] › 2.7/1 rev.4 Clinical evaluation: Guide for Manufacturers and Notified Bodies › 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 › 2.7/3 rev. 3 Clinical Investigations: Serious Adverse Event Reporting 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
21 CFR Part 812 – Investigational Device Exemptions[6]	Member State Requirements
21 CFR Part 814 – Premarket Approval of Medical Devices[7]	Declaration of Helsinki
ISO 14155:2011 – not required, but FDA recognizes the principles it represents	ISO 14155:2011; ISO 9001; ISO 13485

ISO 14155:2011 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.[8] While ISO 14155:2011 is not part of the official U.S. Food and Drug Administration (FDA) regulatory requirements for medical devices, the FDA recognizes the principles it represents.

Recent updates in the U.S.

The 21st Century Cures Act enacted in December 2016 includes a number of provisions that impact medical device sponsors:

Figure 2. 21st Century Cures Act device provisions[9]

Provision/Summary
Breakthrough Device *(Section 3051)* Establishes an expedited review program for devices intended to treat or diagnose life-threatening or irreversibly debilitating diseases or condition; similar to the existing Breakthrough Designation program for drugs and biologics and applies to 510(k), de novo petitions and premarket approval applications (PMAs)
Recognition of Standards *(Section 3053)* FDA required 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)* FDA required to publish every five years a list of Class I and II devices that no longer require 510(k) clearance
Institutional Review Board Flexibility *(Section 3056)* Removes the requirement that local IRBs must approve device trials

Recent EU Updates

In June 2016, partly in response to high-profile breast implant and metal-on-metal hip implant scandals, the European Commission published proposed revisions of its Medical Device Directives (MDD). These revisions – now regulations, rather than simply directives – help address the need for a robust, transparent, predictable, and sustainable regulatory framework for medical devices which ensures a high level of safety while supporting innovation. The proposed legislation includes:

+ European Medical Device Regulation (MDR), which would cover devices that previously fell under the MDD and Active Implantable (AIMDD) with a three-year transition period for full compliance
+ European In Vitro Diagnostic Regulation (IVDR), which would cover devices that previously fell under the In Vitro Diagnostics Directive (IVDD) with a five-year transition period for full compliance

It is anticipated that final agreement on the text of the revisions will be reached in March 2017, and that these new regulations will go into effect in May 2017.

Medical device sponsors should be aware of a few key provisions included in these updates:

+ **Stricter requirements for Notified Bodies (NBs)**. NBs are subject to higher accreditation standards, and current NBs must become re-certified under these new standards. In addition, NBs are required to perform unannounced manufacturer and supplier audits.
+ **Stricter requirements for the level of clinical evidence required to support medical device assessment**. All Class III devices and implants require clinical investigations, and equivalence demonstrations are no longer accepted. Increased documentation is required, including a Clinical Expert Report that covers the entire product lifecycle. There is also greater emphasis on comparative device evaluation, and sponsors will need to get agreement from the manufacturer of the comparative device to include it in the investigation.
+ **IVDR provides a new classification system and requirements for IVDs**. In vitro diagnostics 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.
+ **Companion diagnostics are regulated for the first time under the IVDR**. Competent authorities will be involved in this evaluation and regulation.

Device Development Process

In 2013, the FDA issued a 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:[10]

Device complexity. An understanding of the scientific principles underlying device function and mechanism of action may be relevant in assessing performance and the 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 skillsets or personnel are required for 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, then study personnel should not be trained in the use of the device to ensure that the study reflects intended use conditions.

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

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

Similar to drug development, there are five basic steps involved in medical device development:[9]

1. **Discovery**. Once a device has been invented, it must be classified, as the development process is dependent on the device's classification. Sponsors should keep in mind that the classification of a device may differ in the U.S. and the EU (see Figure 4 and Figure 5).
2. **Preclinical research**. During this step, researchers build a prototype of the device which is not for human use. This prototype is tested in a controlled laboratory setting and it is refined based on the data gathered to reduce risk of harm in people.
3. **Clinical research**. The device is tested in people to ensure that it is safe and effective. Sponsors should note that the stages and sizes of medical device studies are different than drug studies (see Figure 6). For device trials in the EU, as of 2010, all serious adverse events (SAEs) must be reported to the relevant Competent Authority (CA) and Ethics Committee (EC). However, it is important to keep in mind that when considering device safety, it is crucial to determine whether an event was caused by the device or not. Device deficiencies should be reported as well if they could have led to a serious adverse device effect (SADE), or an SAE that is related to the device or the procedure.
4. **Regulatory review**. Clinical data is reviewed by the relevant regulatory authority for approval or non-approval.
5. **Post-marketing surveillance**. The relevant regulatory authority monitors device safety after the device is available for use by the public. For post-marketing trials in the EU, where the device falls under MDD, only SADEs need to be reported.

Investigational device exemptions vs. investigational new drug applications

There are a number of similarities in the requirements for investigational device exemptions (IDEs) and investigational new drug (IND) applications.

Figure 3. Requirements for IDE and IND

	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 labelling requirements	✔	✔
Addresses waivers	✔	✔
Describes investigator responsibilities	✔	✔
Requires selection of qualified investigators	✔	✔
Requires study monitoring	✔	✔
Requires IRB approval prior to initiating the study	✔	✔

A notable difference is that IDEs require hands-on device training and in-depth protocol training for investigator site staff because the efficacy and safety of the device may be highly dependent upon the technique applied. In addition, not all adverse events are reportable under an IDE due to the local effect of the device.

Stages of Medical Device Clinical Investigations

If clinical evidence is required, medical devices may undergo three general stages of clinical investigation, which may be extremely dependent on each other. As such, performing a rigorous evaluation in one stage can make the next stage more straightforward.

Figure 4. Stages of Clinical Development: Device vs. Drug

Device Studies	Drug Studies
Pilot or exploratory: Small study (10-30 patients with the condition) to determine preliminary safety and performance	**Phase I:** 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 II:** Larger study (up to several hundred people with the condition) to establish clinical proof of concept, preliminary efficacy, and characterization of adverse effects
Post-approval: Post-approval study to collect long-term data	**Phase III** *(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
Note: Not all devices will go through all stages	**Phase IV:** Post-marketing study to collect long-term data

Classification of medical devices

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

In the U.S., classification is determined by the U.S. Food and Drug Administration.

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

+ **Determine the applicable directive**. The manufacturer is responsible for determining which directive is applicable to the device: Medical Devices Directive (MDD), Active Implantable Medical Devices Directive (AIMDD), or In Vitro Diagnostics Directive (IVDD). Most devices fall under the MDD.
+ **Determine the class**. Each directive 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.

The risk-based classification system in the EU considers the following key factors:

+ Duration of patient contact
+ Degree of invasiveness
+ Activity of the medical device
+ Therapeutic area, particularly cardiovascular or central nervous system

Figure 5. Medical Device Classification in the U.S.[12]

U.S.			
	Class I	**Class II**	**Class III**
Description	Low risk	More 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 prosthesis › Single-use scalpel	› Pacemakers › Breast implants
Clinical trial required?	No	Maybe	Yes

Figure 6. Medical Device Classification in the EU[13]

EU	
	Example
Reusable surgical instruments	› Low › Low/medium
Surgically invasive devices intended for transient use	› Medium
Blood bags	› Medium/high
Surgically invasive devices in contact with the CNS	› High

Applying ISO to Device Trials

Globally-accepted standards such as ISO 14155:2011 define the principles of good clinical practice and help to protect the rights, safety, and well-being of human subjects. Per ISO 14155:2011, clinical data is needed to demonstrate that a device is safe, performs as intended, and has an acceptable risk/benefit ratio. Generally, in the EU, even Class I devices require clinical evidence demonstrating that the level of device effectiveness consistently and accurately meets requirements for the labeled application. This clinical data may include bench testing, a compilation of relevant scientific literature, and/or a clinical trial in human subjects.

The need for clinical data from prospective clinical trials is typically needed when:

+ Components, features, and/or method 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 for which there is no prior clinical experience
+ An established device is proposed for a new indication

To maximize the likelihood of success at every stage of development, a medical device trial should be designed to meet ISO 14155:2011 guidelines.

The principles set forth in ISO 14155:2011 also apply to investigations for non-regulatory purposes. In these cases, the requirements of this international standard should be followed as far as possible. For Post-Marketing Surveillance (PMS) studies, there are fewer requirements and monitoring activities, but it may still be advisable to follow ISO standards as NBs and regulatory bodies are putting increased emphasis on PMS studies. Sponsors should check with national regulations, as some optional requirements may be obligatory in certain Member States.

Approval Pathways

In the U.S.

In the U.S., the responsible regulatory agency for medical devices is the FDA's Center for Devices and Radiological Health (CDRH). The pathway to approval 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:

+ **Exempt from premarket submission**. This applies to most Class I devices
+ **Premarket Notification** [510(k)]. This applies to some Class I and most Class II devices
+ **Premarket Approval (PMA)**. This applies to most Class III devices
+ **De Novo (Evaluation of Automatic Class III Designation)**. This applies to new devices without a valid predicate that would otherwise be classified into Class II or III
+ **Humanitarian Device Exemption (HDE)**. This applies to Class III devices intended to benefit patients with rare diseases or conditions

Of note, the FDA recently issued draft guidance on the use of real-world evidence to support regulatory decision-making for medical devices.[14]

In the EU

In the EU, devices are put on the market following risk-based conformity assessments which typically involve a Notified Body hired by the sponsor. Notified Bodies are independent commercial organizations that are designated, monitored, and audited by the relevant EU Member States via the national CAs. Recent changes to EU regulations have increased the requirements and rigor with which CAs review Notified Bodies, which has resulted in a decrease in the number of Notified Bodies.

The relevant Medical Device Directives – soon to be regulations – define the conformity assessments required for devices, depending on their classification, and the pathway to market is a CE marking.

Figure 7. Steps Involved in Obtaining Market Approval in the U.S. and the EU

	U.S.	EU
Step One	Determine classification of the device	Determine device classification and the applicable EU Directive: › Active Implantable Medical Device Directive (AIMDD) › Medical Device Directive (MDD) › In Vitro Diagnostic Medical Device (IVDMD)
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 a CE marking Technical File or Design Dossier and implement a quality management system (QMS), if applicable. Generally, companies use ISO 13485 for their QMS requirements.
Step Three	Prepare a Premarket Submission to the FDA	Have the Technical File/Design Dossier and QMS audited by a Notified Body
Step Four	Submit the Premarket Submission and interact with the FDA during review	Obtain CE marking and ISO 13485[15] certificates (if appropriate) from Notified Body
Step Five	Complete the Establishment Registration and Device Listing	Prepare of Declaration of Conformity (DOC) which states that the device complies with the appropriate Directive

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 in 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 on the horizon, so it is critical for sponsors to stay informed and up to date. Sponsor responsibilities for running clinical investigations have increased, and areas such as informed consent, risk assessment, monitoring, document control, and electronic data management have become better defined, with more stringent requirements. Working with a contract research organization (CRO) with device experience, the capability to build quality by design into a clinical trial program and a track record of success can help sponsors improve data transparency and navigate the device development process more smoothly and with greater success.

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Joanne Emmett | Vice President, Medical Device

With over 20 years of clinical research industry experience, Joanne has a keen focus on operational design and delivery. She began her career in academia within transplant and then cardiovascular research. She joined the CRO space in 1995 and was engaged as a CRA, LCRA and Project Manager on trials in CNS, Oncology, Respiratory, Cardiovascular Device and several diagnostic programs. Joanne then moved into oversight and leadership specializing in Clinical and Project Management Delivery, spending time at PRA before joining Premier Research in early 2011. Since then, Joanne has overseen the operational delivery structures and planning for both clinical and project management. She has focused on the key needs and standards within therapeutic areas and medical device and ensuring core process designations for staffing and oversight.

Nicky Dodsworth | Vice President, Quality Assurance, Risk, and Compliance

Nicky Dodsworth is currently Vice President Quality Assurance, Risk & Compliance for Premier Research with responsibility for pharmaceutical and medical device studies. Nicky is an active member of European Forum for Good Clinical Practice (EFGCP) and, in 2010, she started to run the EMWA Workshop on Quality Awareness in CSR Development. She is also a Senior Associate Member of the Royal Society of Medicine and a Chartered Scientist, an award from the Science Council in the UK bestowed on professional scientists who are practicing and/or advancing science as an integral part of their daily work.

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North America: **+1 919 627 9069**
Europe: **+44 118 936 4000**

info@premier-research.com
premier-research.com