Implantable medical devices:

Preclinical testing in new product development – On the road to clinical reality

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Abstract

Implantable medical devices (IMDs) have restored viable and meaningful lives to millions of people who would have otherwise continued to be severely restricted or suffered early death due to their pathologies. Research and development of IMDs are complex and time-consuming and market authorisation is regulated by country laws and regional regulations to provide safe, effective, and reliable products to patients. Due to their invasive nature, IMDs are considered to be high-risk devices that require extensive preclinical research and testing. Current early development phases and their associated requirements are reviewed.

Implantable medical devices (IMDs) have been used globally for decades in established and unique clinical settings to restore anatomical and physical functions, improve quality of life, and save human lives. More recently they are achieving prevention, monitoring, and diagnostic functions and are replacing or complementing pharmaceutical therapies. The development of medical devices for commercial use is a complex process that involves considerable time and expense. This article will provide an overview of IMD product development through preclinical testing for the purpose of regulatory approval and commercialisation.

IMDs are introduced into the human body either surgically under direct visualisation and/or through minimally invasive medical interventions using external visual control. Many of these technologies are referred to as "revolutionary" or "breakthrough" inventions or novel applications of existing technologies. In some cases, they are also considered to be "disruptive" to currently accepted treatments or standards of care and may require the qualification of new medical subspecialties. With the introduction of new materials, processes, techniques or system designs some marketed IMDs have substantially changed and can also require new regulatory approvals. Transcatheter heart valve implantation using transfemoral or transapical heart access is a recent

example of a disruptive/breakthrough therapy where the redesign of existing surgical biological heart valves and catheter delivery systems enabled the less invasive introduction and implantation of an artificial heart valve into the beating heart without opening the chest, using a heart-lung machine, or suture fixation of the device.[1]

Medical device regulation

To optimise device evaluation, testing results, and their presentation in a regulatory submission it is essential to understand product development phases and processes, the appropriate international standards guidelines to follow, as well as the regional regulatory requirements.

Bringing new IMDs to patients and commercial markets is governed by country laws, and regional regulations such as the European Union Medical Device Regulation 2017/745 (EU MDR) and the Federal Food, Drug, and Cosmetic Act that is administered by the Center for Devices and Radiological Health (CDRH) of the United States Food and Drug Administration (US FDA). The main purpose of medical device regulation is to evaluate their safety, effectiveness, quality and reliability for target patients. International standards evaluating these areas of interest have been developed by the International Organization for Standards (ISO). The standards are voluntary but can be required in some countries' medical device regulations. There are several ISO standards that are specific to medical devices and provide guidance to manufacturers and regulators in areas such as quality management systems including product design & development (ISO 13485:2016), application of risk management to medical devices (ISO14971:2019), and clinical investigations of medical devices in human subjects (ISO 14155:2020). As part of the transition to the EU MDR, old "MEDDEV" guidance documents are being replaced. New documents are endorsed by the Medical Device Coordination Group (MDCG) in accordance with Article 105 of the EU MDR. These guidance documents are available on the European Commission Public Health Medical Devices Section website and address many aspects of medical device regulation.[2]

In the past, IMDs were able to be studied and introduced in the European Union noticeably sooner than in the United States. The EU MDR has modified many regulation articles that can lengthen the submission process. The US FDA has, however, recently initiated a new Breakthrough Devices Program and Guidance document (December 2018) to expedite the market availability of novel medical devices but retains the statutory premarket approval standards. This programme offers manufacturers access to FDA experts to ascertain how to study the device and which regulatory path to use. A Breakthrough Designation request can be sent to the FDA any time before sending a marketing submission.[3,4]

Medical device classification

The regulatory approval process classifies medical devices according to the type of bodily contact, the duration of contact with the human body and their associated biological effects or risks into Class I (low risk); Class II (moderate risk) (in EU Class IIa – short term use; Class IIb – long-term use) or Class III (high risk) devices. The risk classification of the device will determine its path to market. In the EU, prior to classifying a device, documented statements must be developed that are required for the Technical Documentation file. The EU MDR, Annex II, 1.1, indicates the specific elements of device description and specification along with other product features that can assist in deciding on which risk classification the device will receive.

IMDs in direct contact with tissue, bone, or blood are defined as being high risk, Class III devices and require extensive preclinical testing and clinical trials in the EU and US. In the EU, medical devices can be commercialized after receiving CE marking. (See EU MDR 2017/745 Annex VIII for definitions, rules, on the classification of medical devices, and MDCG 2021-24, October 2021 Guidance on classification of medical devices.) In the United States, market authorisation is granted for Class III medical devices following Premarket Approval (PMA), for Class II devices with a Premarket Notification 510(k) clearance, for some low to moderate risk devices with a De Novo classification, defined as those devices for which there is no legally marketed predicate device or with a Human Device Exemption (HDE) for patients with rare diseases or conditions. To learn more about FDA Medical Device Classification a web-based tutorial is available on CDRH Learn. (How is My Medical Device Classified? CDR Kimberly Piermatteo, MHA).[5] Table 1 shows device risk classifications with definitions, examples, and the requirements for market authorisation in the European Union and the United States.

Medical device development phases

Medical product development can be divided into 5 phases:

1. Ideation/discovery;
2. Preclinical research including design specification, prototyping, bench performance testing and *in vitro* and *in vivo* testing;
3. Human clinical trials;
4. Regulatory preparation, review and submission; and
5. Post-market surveillance. Each of these phases will have different timelines depending on the product risk classification and extent and depth of preclinical testing and clinical trials results.

The team should include representatives from engineering research and product development, animal testing, medical/clinical affairs, medical writers, quality, safety, regulatory, manufacturing, packaging, labelling, product management, and marketing.

New product development team

To reduce communication barriers between device manufacturer departments and improve regulatory submission processes, a project-specified new product development team should be created incorporating members from various stakeholder departments. The team should include representatives from engineering research and product development, animal testing, medical/clinical affairs, medical writers, quality, safety, regulatory, manufacturing, packaging, labelling, product management, and marketing. A diverse interdisciplinary team will provide a wide range of knowledge and experience that can expedite discussions within and between departments, offer suggestions and generate questions on new findings. Team leaders are traditionally chosen from the engineering and product development group who are responsible

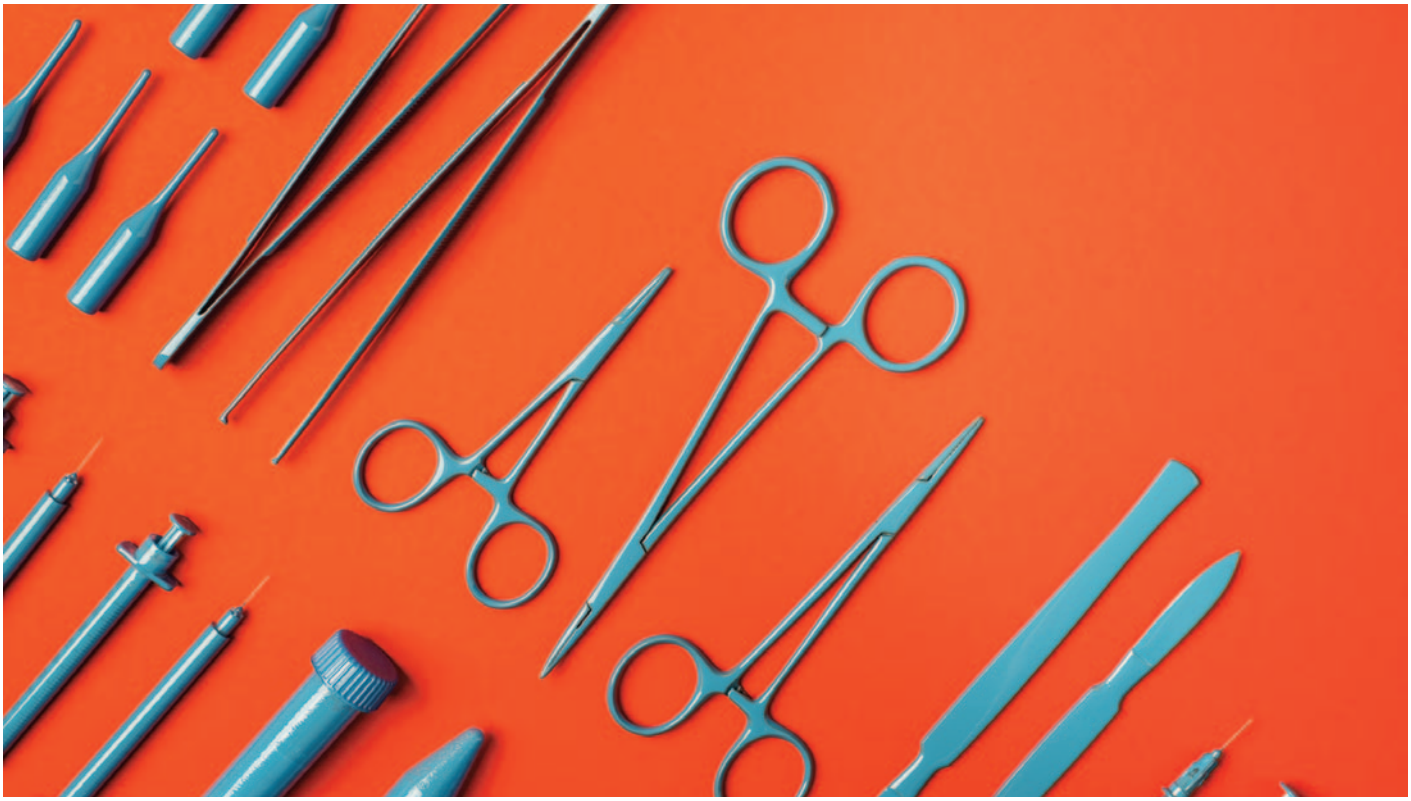
Table 1. Medical device classification and requirements for market authorisation in the EU and US

System	Class	Risk	Definition / Examples	Market Authorisation Requirements
EU	**I Basic**	Low	Non-invasive devices that do not interact with the human body, non-sterile. no measuring function / Wheelchair, plaster, hospital bed, bedpan, compression stockings	No, self-documentation with CE mark and identification code (UDI)
Sub-categories	**Is**	Low	Sterile market placement / Personal protection kits	Partial, CE marking
	Im	Low	Devices with a measuring function / Stethoscope, thermometer, weight scale	Partial, CE marking
	Ir	Low	New subclass for reprocessed or reused products / Surgical instruments, endoscopes	Partial, CE marking
	IIa	Moderate	Inserted in the body short term (60 minutes to 30 days) / Hearing aid, ultrasonic diagnostic device, indwelling catheters, cannulas, tracheal tube	Yes, CE marking
	IIb	Moderate to high	More complex than IIa devices, inserted or implanted > 30 days / Infusion pump, intensive care monitoring equipment	Yes, CE marking
	III	High	In direct contact with central circulation, nervous system or contains a medicinal product / Pacemaker, prosthetic heart valve, cardiovascular catheters e.g. angioplasty catheters, stent delivery catheters, neurovascular coils	Yes, CE marking
USA	**I**	Low	Present minimal potential for harm / Manual stethoscope, adhesive bandages, crutches, tongue depressors	510(k) exempt, 510(k)
	II	Moderate	Higher risk than class I devices / Syringes pregnancy test kits, platelet rich plasma separation kits, electric wheelchair	Premarket Notification 510(k) or De Novo, with or without Breakthrough Designation
	III	High	Sustain or support life, are implanted, or present potential unreasonable risk of illness or injury / Intraocular lens, artificial heart valves, pacemakers, implanted prosthetics	Pre Market Approval or Human Device Exemption with or without Breakthrough Designation

for managing information within the team and to company leadership. One should however consider the rotation of team leaders or identify team co-leaders with members who have expertise in the actual development phase. This can improve focus on the relevant goals and timelines in that phase and better address issues or areas of concern. For example, when it is time to develop clinical trial protocols and prepare for human clinical trials, a medical/clinical affairs member of the team would be in a better position to interface with and direct the team rather than someone from the engineering group. Team leader rotation supports growth in member expertise, encourages creativity, and helps develop new leadership skills and motivates team member involvement.[6]

New product discovery

Ideas for new medical devices usually arise from the need to treat or alleviate unmet clinical challenges of diseases in a larger patient population. Often clinicians who have considerable knowledge and experience with a specific disease entity will develop ideas to improve patient outcomes. Their patient observations and early research are key for successful collaborations with the medical device industry to participate in early evaluations and define medical device engineers' initial device concepts, designs, and materials. In the discovery phase, consideration has to be given to anatomical structures, biological reactions, clinical complications, engineering issues, material availability and mechanical limitations. Medical device engineers may have to be knowledgeable in a variety of fields that may include biocompatibility, structural design, electromechanical systems, delivery systems, power management and wireless communication. A complete review of the relevant scientific and medical literature including *in vitro* and *in vivo* animal research and human trial experiences and will be of significant help in understanding the underlying disease process,



current standards of care, device inputs and designs, compatible materials as well as clinical results of similar marketed devices and should be available for submission.

Devices implanted surgically may need new instruments or implant accessories whereas minimally invasive techniques will require additional instruments or delivery devices to bring them to the correct target organ or anatomical location. Changes in visualisation techniques for successful implantation can also be necessary. For example, in transcatheter therapies for structural heart disease the evolution of multimodality imaging such as real-time 3-dimensional echocardiography, computer tomography angiography and 4-dimensional technologies now enables more reliable pre-procedure planning, accurate procedural placement and post-procedural follow-up of these devices.[7,8] Adjunct devices will also need development or modification documentation and testing, and regulatory approvals. These documents must also be included in the regulatory submission of the implantable device and may require separate approvals.

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Design control

Design control is an integral part of product development to ensure that the medical device being developed is safe. The intent of design control is to avoid undocumented changes, improve predictability and reduce unanticipated surprises during product development and production. The FDA first included design control require-ments in their medical device approval processes and the current version is found in the FDA 21 CFR (Code of Federal Regulations) Part 820.30. In the EU MDR, design control is incorporated in the manufacturer's quality management system addressed in Annex I, Chapters 1 and 2. ISO 13485:2016 includes design control in section 7.3 and FDA regulation 820.30 is in full alignment with this ISO.

Several distinct phases are incorporated into the design control framework:

1. Design planning with the designation of user and patient needs,
2. Design input,
3. Design output,
4. Design verification, and
5. Design validation. A design history file is required to maintain all documentation of records and show that the device design was developed in accordance with the approved design plan and requirements.

In phase 1, the user needs to identify the intended use of the product, indications for use and the patient population. The intended use is the purpose of the device, the indications describe the disease state or the disorders that the device will diagnose, prevent, alleviate, or cure. Design inputs are design features that are measurable and include all physical, functional, safety and performance requirements of the device. Inputs can be driven by guidance documents, predicate devices, competitive products, industry standards or risk analysis. Design inputs descriptions must be clear and

concise and are tested to "pass/fail" criteria.

Design outputs show that the design input features have been implemented and can be used as guidance documents for device production and assembly. Examples of these documents include device and component specifications, manufacturing procedures and assembly instructions, engineering drawings, and engineering/research logbooks.

Design verification demonstrates that the product was made correctly and consistently meets the design input requirements. Test reports must be documented with objective evidence in the design history file and confirm that the design output meets the design input. Design validation ensures that the correct product was consistently manufactured and meets all the identified user needs and intended uses.

Preclinical research and testing

Device prototyping is necessary to identify the optimal design, compatible materials and processes of device manufacture. Most early prototypes are produced by hand, may go through several iterations and not always be constructed from final production materials. Physical simulations using non-clinical bench performance tests are conducted to validate the plausibility of the device concept under anatomical and physiological conditions. These tests can cover mechanical and engineering performance evaluations such as fatigue testing, material wear, tensile strength, compression, and burst pressure. Tests are performed using *ex vivo*, *in vitro*, *in situ* animal or human tissue, animal carcass, or human cadavers. All testing is to be governed by documented protocols. Regulatory submissions require complete test reports including all tests performed, test objectives and methods, pre-defined pass/fail criteria, results summaries, discussions, and conclusions. A table of test summaries is also often requested by regulatory bodies. The overall objective is to demonstrate substantial equivalence of the new IMD to a predicate device or reasonable assurance of safety and effectiveness of the IMD and that it can be durable and consistently produced for human use *before* implanting it in a human.

In the early design phase, bench testing can pinpoint potential design and mechanical flaws and check on the performance and safety of the device. After the initial design has been finalised, bench testing will document that the device is meeting the design specifications. When pre-production prototypes or production units are available, they will also be tested to show appropriate safety and performance. Technical testing of materials and electronic components is also included in the proof of concept testing. Testing strategies for bench testing should be carefully reviewed by the product development team to make sure all required and appropriate tests are transparent and complete. This includes test results for pre- and post-marketing requirements such as comparative testing with earlier models, with other similar marketed models or for marketing brochures and labelling.

Following bench and technical testing, the materials and/or IMD must undergo further biological evaluations and biocompatibility testing to demonstrate that it will perform its intended function without causing any short-term or long-term adverse effects to the human body such as cytotoxicity, mutagenicity and genotoxicity, haemocompatibility irritation, sensitization, acute systemic toxicity, subacute chronic toxicity, carcinogenicity, or material-mediated pyrogenicity. *In vitro* and *in vivo* animal testing are often performed to evaluate the interaction between the IMD and body fluids, cells or tissue of the recipient. The animal models chosen for IMD testing will be dependent on the device materials and IMD implantation location. The FDA has also recently released guidance documents that are focusing on improved efficiency of medical device testing and the implementation of well-designed large animal studies to be used to leverage safety tests such as systemic toxicity, chronic implantation and *in vivo* thrombogenicity and thereby replace the traditional small animal model.[9] The ISO 10993 – *Biological evaluation of medical devices* consists of a series of 20 guidance documents that can help the manufacturer select the most appropriate tests to screen for device biocompatibility to manage biological risk. Part 1 of ISO 10993 defines and describes the applicability of the additional 19 parts and the necessity to evaluate results within a risk management process. Attachments A through F of ISO 10993-1 provide very relevant recommendations, examples and summaries of reports to be written for the biocompatibility section of the regulatory submission.

A final important element of the early design phase is the creation of a risk management plan and assignment of a team that is knowledgeable about the construction, function, production and use of the medical device and risk management tasks. Risk management is now mandated by EU MDR in Article 10(2) and is described in Section 3 of Annex I. The US FDA 21 CFR 820 also addresses risk management in their Quality Systems regulations. Both use the ISO 14791:2019 *Medical Devices – Application of risk management to medical devices* as their guidance document. The purpose of risk management is to make sure that the medical device is safe which is defined as having a product that is free from unacceptable risk.

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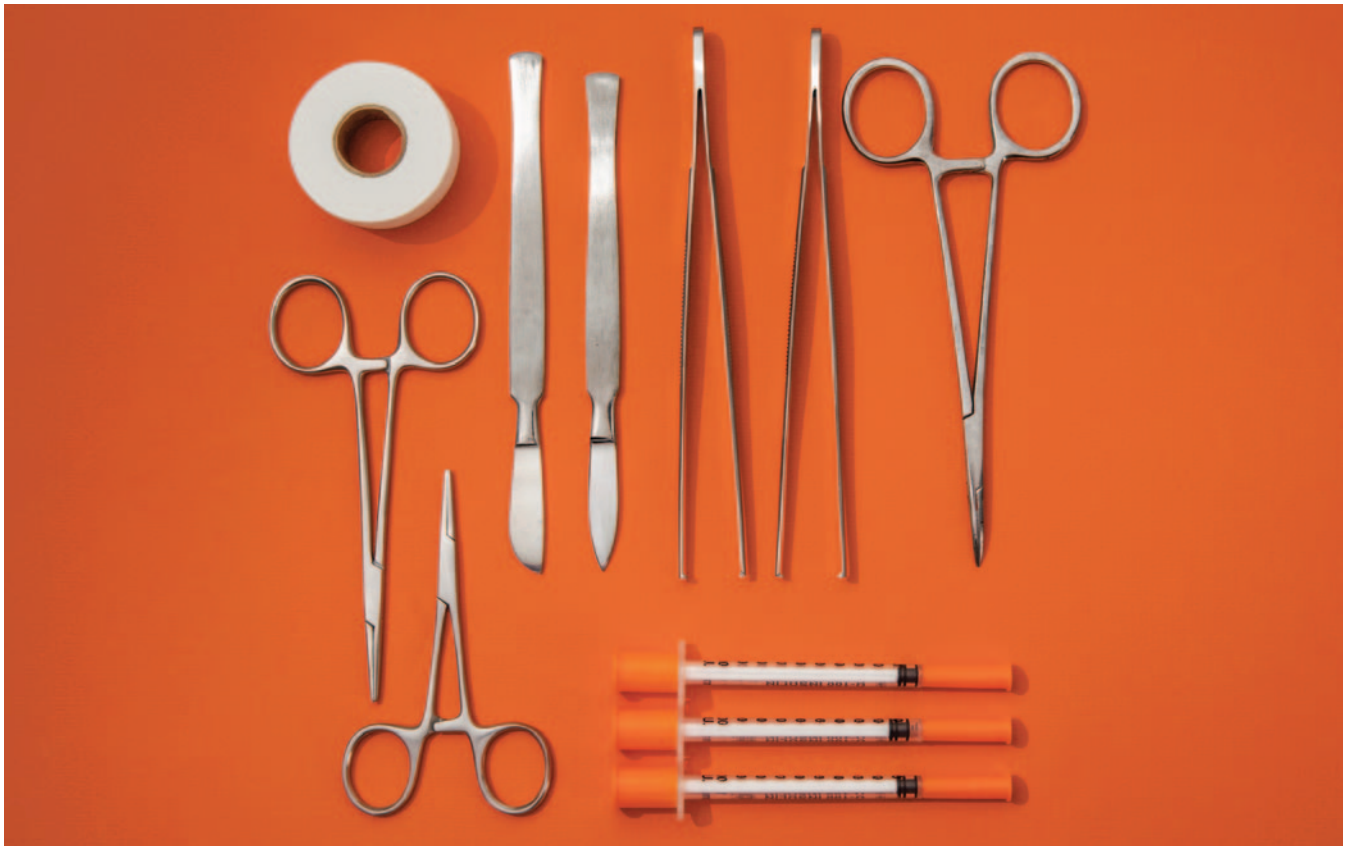
The risk management process is active throughout the product life cycle of all medical devices from product design and development to final market withdrawal. Most medical device manufacturers have been managing risk with a Failure Modes and Effects Analysis (FMEA) (IEC 60812:2006) that has traditionally been managed by device engineering groups. Design FMEAs however specifically look at component failures and their consequences and identify how to mitigate the failure risk. This is only part of the overall risk management process. Risk management as per ISO 14971 focuses on the identification and analysis of known and foreseeable product hazards and resulting human harms, followed by a calculated estimation of the acceptability of the risk. Thereafter risk control options, risk control measures, and residual risk are identified and verified. This analysis is best documented in a dynamic hazards matrix that requires regular review and updates especially when new information is available such as production data, complaint information, post-market surveillance, medical literature and clinical evaluation report updates. A risk management file must also be established that contains relevant records and documents from the ongoing risk management process that can be submitted with a regulatory submission or presented to a regulatory auditor.

Developing new and innovative IMDs is an exciting but challenging and often resource-intensive endeavour. To keep new products in the pipeline a company has to commit to a culture



where innovative ideas are nurtured and quickly initiated and where the company infrastructure is committed to the development and pre-clinical phases knowing that risks of failure may be high. Despite the recent increase in regulatory hurdles, for a complete and successful IMD submission, the early preclinical phases of IMD development require thorough planning, attention to detail, appropriate and rigorous testing protocols and accurate and complete documentation.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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