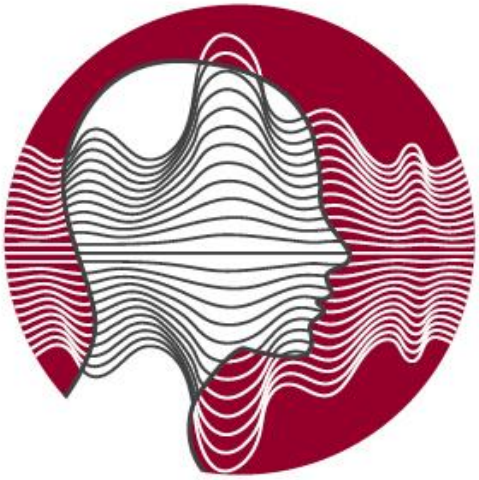


myWAVE

TRANSLATION AND COMMERCIALISATION OF EM MEDICAL TECHNOLOGIES

GUIDELINES AND RECOMMENDATIONS

COST ACTION CA17115 MYWAVE

Working Group 3

INNOVATION TOOLS

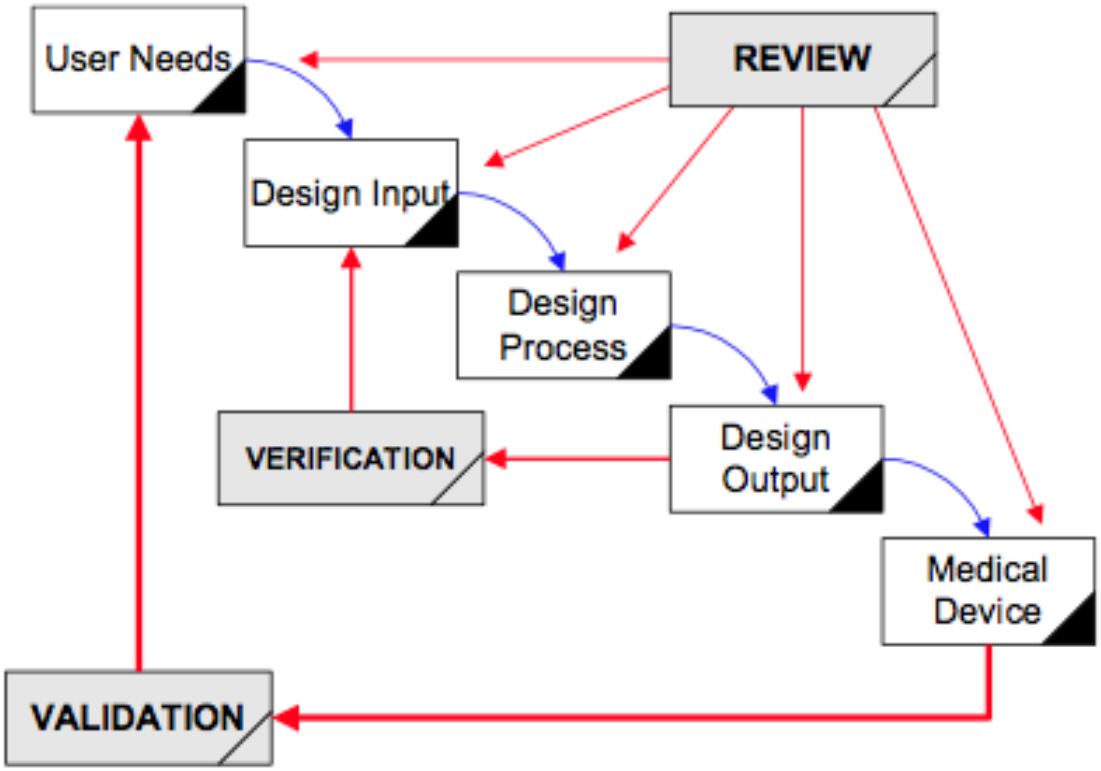
We understand that taking an idea for innovation through to a product that can be used in healthcare systems is challenging. That is why we created this suite of innovation tools on all stages of the innovation pathway from prioritisation to adoption to inform and support all innovators at each stage. These tools can be used as a guide and combined with other resources and knowledge to help you through your innovation journey.

DESIGN STANDARDS

Medical devices are subject to strict general controls and procedural regulations, and the development and use of standards is vital to ensuring the safety and efficacy of medical devices. Numerous regulatory agencies and standards organisations collaborate to establish the accepted standards for medical equipment. The type of device determines the agency (or agencies) to whose regulation it is subject. As a medical device innovator you should have some knowledge of design standards, even though it's a specialised field typically handled by design engineers and quality management systems experts.

What is a design standard?

A standard is an agreed way of making a product, managing a process, delivering a service or supplying materials. Standards can be agreed for all aspects of how we live, from standards for quality, product performance and safety to standards for building design and services. Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments and list their medical devices with the regulatory agency of the country they wish to sell into. Listing of a medical device includes submission of the regulatory documents based on device classification along with submission of compliance towards design standards during the design, development and manufacturing of the device.
You can get more detail on the US FDA regulatory pathway HERE and on US FDA compliance with design standards HERE.



What types of standards are relevant to your medical device and why?

Knowledge of, and conformance to, standards recognised by the national regulatory body is key if you want your device to be approved for sale in a country.
In the US, the FDA department responsible for regulating medical devices and radiation-emitting products, the CDRH, believes that conformance with recognised consensus standards can support a reasonable assurance of safety and/or effectiveness for many applicable aspects of medical devices. A database containing the US FDA's recognized consensus standards from ≈25 standards organisations can be searched so you can find the relevant standards for your product. You can narrow your research by the Standards Organisation you wish to investigate.

Where can I buy or refer to standards?

International Organisation for Standardization (ISO) is a non-governmental organisation that develops and publishes international standards on a wide range of subjects, including medical equipment. The ISO13485 standard establishes the requirements for a quality management system for both the design and manufacture of medical devices. It covers aspects including risk management, design control during product development, and verification and validation systems. You can search for ISO standards HERE.

International Electrotechnical Commission (IEC) is a non-governmental organisation that prepares and publishes International Standards for all electrical, electronic and related technologies. The IEC 60601 is a series of technical standards for the safety and effectiveness of medical electrical equipment. You can search through the IEC standards HERE.

ASTM International American Society for Testing and Materials) is a globally recognised leader in the development and delivery of international voluntary consensus standards. ASTM standards encompass virtually all medical devices and services imaginable – and all aspects relevant to medical devices, such as materials and biological components. ASTM standards encompass product areas including anaesthesia, biocompatibility, cardiovascular, dental, orthopaedics, plastic surgery, general surgery, general hospital devices (such as medical gloves), materials, neurosurgery, obstetrics and gynaecology, sterility in medical devices, and tissue engineering. You can search through the IEC standards HERE.

MDR DESIGN DOSSIER

Medical device companies who wish to sell their devices in the European market must obtain a CE marking. The European Medical Device Regulation (EU) 2017/745 (MDR) requires medical device manufacturers to provide technical documentation for their products. The technical documentation is a compilation of all relevant documents for a product and must be kept up to date throughout the entire product life cycle. It is the basis for the conformity assessment and thus for the CE marking of a product. The MDR has been fully applicable since 26 May 2021. All the steps involved in getting a CE certification are mentioned HERE.

What does a MDR Design Dossier include?

When CE marking a medical device, the manufacturer must present the medical device technical file to the regulatory body. According to Annex II of the EU MDR 2017/745, it should include the following elements:

- Description of the device and its specification, including variants and accessories.
- Labelling and packaging information.
- Instructions for use in all the EU state languages where the medical device is to be sold.
- Design and manufacturing information (details of manufacturing sites, where design and manufacturing activities are to be performed).
- Documentation demonstrating compliance with general safety and performance requirements with regards to relevant standards.
- Detailed risk analysis and risk management file.
- Product verification and validation report and other relevant documentation.
- Pre-clinical and clinical data, such as test results, clinical evaluation report and Post Market Clinical Follow-up evaluation plan.
- Post-market surveillance plan and report.
- Declaration of Conformity.

In addition to the technical file, medical device manufacturers must establish, document and implement a proper quality management system and maintain its effectiveness throughout the lifecycle of the device.
The documentation must always be up to date, including the latest modifications to the medical device or amendments in the MDR and any other relevant regulations.
According to Articles 38 and 39 of the MDR, all documents part of the medical device technical file must be in a language determined by the Member State concerned.

How do I file for CE certification?

According to Annex IX of the EU MDR 2017/745, the technical file of medical devices class IIb and class III must be assessed by a Notified Body for compliance with relevant requirements. In this regard, manufacturers must submit an application for assessment to a Notified Body, which must address the design, manufacture and performance of the medical device in question.
A notified body, in the European Union, is an organization that has been designated by a member state to assess the conformity of certain products, before being placed on the EU market, with the applicable essential technical requirements. These essential requirements are publicized in European directives or regulations.

Where do I find these notified bodies?

A list of notified bodies can be found HERE. Some EU countries have more than one notified body. You may reach out to any notified body across the EU to file for CE certification depending on which country is your target market.

What happens once I get the CE certification?

The Regulatory Authority monitors the safety of medical devices after they are placed on the market. The Regulatory Authority operates a national reporting system for medical devices. If new safety or quality information emerges, The Regulatory Authority ensures that medical device users are informed and advised as needed. They carry out on-site audits of selected manufacturers of medical devices to monitor compliance with relevant standards and legislation. They may also audit in response to a significant medical device safety or quality concern.

If they identify a significant safety or quality concern with a device, there are a range of regulatory actions which can be executed to protect public health. These include changes to labelling, safety notices and recalling the product from the market. They can also request changes or modifications to the device itself.

RESEARCH ETHICS

The goal of clinical research includes development of knowledge that can improve human health, but clinical research participants are placed at risk of harm for the good of others and there is the potential for exploitation of these volunteers. Medical device innovators should become familiar with the ethical guidelines necessary for the protection of patient volunteers and to preserve integrity of the science.

Underpinning good research ethics

What are guidelines and principles for ethical research?

Applying for ethical approval can be daunting for researchers and a thorough understanding of the principles of respect for persons, beneficence and justice (the Belmont Report) are an essential starting point before embarking on the process for ethical approval. Innovators should read "Research ethics application: a guide for the novice researcher" and also the ethical guidelines published by the US's NIH, which cover research ethics aspects such as:

- Social and clinical value
- Scientific validity
- Fair subject selection
- Favorable risk-benefit ratio
- Independent review
- Informed consent
- Respect for potential and enrolled subjects

CLINICAL EVALUATIONS OF MEDICAL DEVICES IN THE EU

Clinical evaluation of medical devices verifies safety and performance for its intended use so that the device can be approved, and CE marked. It is an integral part of the medical device development process, applicable to all medical device manufacturers, and as an innovator you need some basic understanding of this area. Clinical evaluation is a specialist area and as an innovator you should involve experts to assist, since a poorly planned or executed process can be costly and risk a new medical device opportunity.

What regulations and guidelines apply?

- The requirements for medical device clinical evaluations are part of Articles 62 through 82 and Annex XV of the EU MDR 2017/745 (Medical Devices). Useful updates and publications can be found HERE.
- Additional to the above regulations, good clinical practice (GCP), according to ISO 14155:2020 “Clinical investigation of medical devices for human subjects”, must be adhered to.
- Useful Guideline Documents: MEDDEV 2.7/1 Rev. 4 (2016), MDCG 2020-5 and MDCG 2020-6.

Why are clinical evaluations necessary?

Satisfying regulatory requirements is the main reason for undertaking clinical evaluations, to demonstrate the device is safe and effective before placing it on the market, but if existing clinical data are insufficient new data must be generated via a clinical investigation or trial. There are however various are other legitimate reasons for clinical evaluations:

- Market: Healthcare providers, payers and patients all want evidence that a new device provides clinical and health economic benefits before adopting it.
- Venture finance: Investors seek ongoing affirmation that product development is on the right track and that their investment is protected.
- Independent verification: Experts in the field that can verify that a product works in accordance with its intended use and indications provides objectivity and confidence for providers, payers and investors.
- Insight: Clinical tests may reveal issues or even opportunities that may necessitate a design revision.
- Intellectual Property (IP): Clinical investigations are the best way to support IP claims.

Is a clinical investigation/trial always necessary?

Broadly, two approaches exist for a manufacturer to prove safety and efficacy, depending on the nature of the device: (i) Proving equivalence to an existing device, or (ii) presenting data specific to a new device via a clinical investigation.

With the ‘proving equivalence’ route, clinical data of an equivalent or ‘predicate’ device can be used to prove safety and performance of your device under evaluation, and the clinical data can be obtained through literature search and post-market surveillance.

But for this route all the following characteristics must be fulfilled regarding your device:

- Clinical: The device is indicated for use for the same clinical condition or purpose, and

- Biological: The device uses the same materials or substances that will be in contact with the same human tissues or body fluids, and
- Technical: The device is of similar design, is used under similar conditions of use, and has similar specifications and properties.

For the clinical investigation route, the generation of clinical data for the new device under investigation is necessary, and such data can be obtained from clinical investigations/trials and literature search. As a rule a clinical investigation is required for implantable devices and class III devices. The EU MDR 2017/745 does allow for exemptions under certain conditions (refer MDCG 2020-5), but for active implantable medical devices there are no exceptions and a clinical investigation cannot be avoided. For existing, established medical devices in continued use refer to MDCG 2020-6 for the data requirements. Importantly, the generation of data does not end once a device has been placed on the market; The clinical evaluation data must be updated through continuous monitoring of clinical performance and safety. In particular, the product needs to be re-evaluated in the case of technical adaptations and optimisations and data from post-market surveillance of the product (e.g., observational studies) must be considered.

What types of clinical investigations are there?

The EU MDR 2017/745 legislation (MDR) specifically describes the following types of clinical investigations:

- Pre-market clinical investigations: Clinical investigations of devices without a CE mark (Art. 62 of MDR).
- Post-market clinical investigations: Post-market clinical follow-up (PMCF) investigations (Art. 74 of MDR).
- Clinical Investigations undertaken for purposes other than those listed in Art. 62 of the MDR: Refer Art. 82 of the MDR.
- Clinical investigations of medical devices without an intended medical purpose: Refer Annex XVI of MDR for further information.

What about preclinical trials?

As an innovator you will almost certainly consider pre-clinical studies, where a prototype can be tested prior to production and testing in humans.
Preclinical testing may include bench testing, technical testing and animal studies to assess feasibility and biocompatibility, toxicology and other safety concerns. Note that animal research in the EU is regulated under Directive 2010/63/EU on the protection of animals used for scientific purposes. The human studies for new devices - pre-market clinical investigations Art. 62 of MDR - are broadly of two types: (i) Feasibility or pilot study: A small study to test the feasibility of the device by collecting preliminary safety and performance data, guide any necessary device modifications and guide pivotal study design; (ii) Pivotal study: A large, statistically driven study to confirm clinical efficacy, safety and risks. Post market studies: Monitor the long-term effectiveness, safety and usage in the general population.

Where do I learn about trial design?

The design of the medical device clinical investigation must generally follow two principles: The well-being of subjects (minimal risks and minimal impairments), and the generation of scientifically valid, reliable, and robust clinical data. The basis of the medical device clinical trial is the clinical investigation plan (CIP) including information about type, structure, and parameters. The structure of the CIP is defined in Annex XV Chapter II of the MDR. The clinical trial must reflect “latest scientific and technical knowledge” (MDR Annex XV I 2.1). The clinical methods must be appropriate to the investigational device (MDR Annex XV I 2.2) and consider technical and functional features of the

investigational device regarding safety and performance (MDR Annex XV I 2.5). Finally, to obtain scientifically valid results, a sufficient number of subjects must be included. Thus, the sponsor must calculate the sample size based on plausible success criteria. Moreover, the clinical environment must be representative for normal conditions of use (MDR Annex XV Chapter I 2.1 and 2.4). Medical device clinical trials must be in line with the CIP as referred to in MDR Annex XIV Part A. A document called a Clinical Evaluation Report (CER) is where the results of the Clinical Evaluation Plan (CEP) process is defined which leads to the analysis and conclusions which is then recorded and documented in the report. It is required for every EU medical device class.

THE GENERAL DATA PROTECTION REGULATION (GDPR)

As a medical device innovator, it's important you are aware of GDPR and that non-compliance carries serious penalties. Therefore you should dedicate time and resources to it, as appropriate.

What is GDPR?

The General Data Protection Regulation (GDPR) Regulation (EU) 2016/679 became effective on 25 May 2018, superseding the previous EU privacy law EU Directive 95/46/EC. Its main objectives are to strengthen the rights of individuals, and to streamline the rules and regulations, with respect to the protection, processing and movement of Personal Data by other people and by organisations across the EU. In particular, Article 8(1) states that "everyone has a right to the protection of personal data concerning him or her". Data subjects have the right to be forgotten, rights around the portability of their data and the right to object to their data being subjected to automated decision making. GDPR does not apply to anonymous data or data related to deceased persons.

GDPR is extra-territorial and applies to any organisation that collects or processes personal data of individuals inside the EU, regardless of where such organisations are located. It covers EU residents and non-residents residing in or visiting the EU while they are in the EU and makes provision for fines of up to €20 million or 4% of global turnover for serious breaches of the law. GDPR is not specific to medical devices but is the legal framework in the EU for the processing of health data, which the GDPR defines as any personal data relating to the physical or mental health of an individual, including any health care service which may reveal information about the person's health status. Therefore GDPR imposes a burden on innovators in medical devices and/or medical software that deals with patient data.

What are the fundamentals of GPRR?

- Data protection language.
- Special categories of data and limits on processing.
- The obligations of organisations with respect to the controlling and processing personal data.

You should also become familiar with data protection principles. i.e., personal data should be:

- Processed lawfully, fairly and transparently.
- Collected for specified, explicit and legitimate purposes and be processed in a compatible manner.
- Accurate, relevant and limited to what is necessary for purpose.
- Kept up-to-date, and inaccurate data should be rectified without delay.
- Securely stored and protected against unlawful processing and accidental loss, destruction or damage.
- Stored for no longer than necessary for the purpose for which it is required, especially where personal data is in a form that identifies the data subject. (Exemptions may apply).

A good starting point for adopting GDPR principles is simply to adopt the approach of 'Privacy by Design', i.e., think about data protection from the outset, viewing it holistically and implementing privacy by design in all processes.

Does GDPR apply to me?

Innovators working to develop and commercialise a medical device will need to comply with the EU medical device regulations EU MDR 2017/745 or EU IVDR 2017/746 irrespective of GDPR. However, if your medical device or medical device software collects personal data, then GDPR compliance is a prerequisite for compliance with MDR or IVDR. Building an MDR/IVDR compliant application requires a suitable Quality Management System and GDPR-compliant technology. HERE is a useful resource: "Ultimate Guide to ISO 13485 Quality Management System (QMS) for Medical Devices".

What are the data technology considerations for GDPR?

Since you are legally responsible for the lawful and safe processing, management and storage of the data you must implement various physical, technical and administrative requirements for GDPR. Physical requirements include facility protection, firewalls, virtual machine security, and system administration. Technical requirements are the most challenging and include data encryption, authorisation and access control, consent tracking, and immutable audit logs. Lastly, administrative requirements include privacy policies, terms and conditions, and GDPR Data Privacy Impact Assessment, and risk impact assessment.

What about health, genetic or biometric data?

This data is a 'special category of personal data' under GDPR, meaning it is considered particularly sensitive as its misuse poses greater risks to data subjects. As an innovator, if you are developing a DigiHealth product you should take care if processing this category of data. Appropriate data protection technical measures including pseudonymisation and encryption.

Who manages the data?

The data controller determines the purposes, conditions and means of processing of personal data. You need to identify the data controller or joint data controllers for your medical device. The data controller is responsible for ensuring compliance with the principles of GDPR. A Data Protection Impact Assessment (DPIA) is used to identity and mitigate against data protection risks. DPIAs are mandatory for new high risk processing projects. A data processor may process data on behalf on the data controller.

Do I need to obtain patient consent?

To comply with the lawful processing of special category data DigiHealth companies might typically rely on obtaining 'explicit consent' from the customers or users of their device or App. But be aware that 'consent' is interpreted in a specific way for the purposes of the GDPR. i.e., it must be given by a clear affirmative act, be freely given, and be specific, informed, and unambiguous.
Privacy notices must provide clear, intelligible and concise information to individuals on what personal data is collected, and how that data is processed. When dealing with vulnerable adults or children, information about data processing must be especially transparent.

How does GDPR apply to clinical investigations?

The EU Commission states that "… it is the obligation of the data controller to implement the appropriate technical and organisational measures to ensure and be able to demonstrate that the personal data are processed in accordance with the data protection rules". Recently, the EU Commission published a Q&A document on the interplay between the Clinical Trials Regulation and GDPR.

INTELLECTUAL PROPERTY (IP)

As a medical device innovator, you will want to ensure no one else can manufacture, sell or lay claims on your product being their idea. Developing strong IP around your device is of utmost importance.

What exactly is included in IP?

Patents: A grant of exclusive rights from the government to make, use, sell, or import an invention.
Trademark: A word, phrase, or symbol that is consistently associated with a specific product or medical method and gives the holder exclusive rights to use a word, phrase, brand name, tagline, or logo.
Copyright: The granting of authors and artists of written and graphical materials the right to prevent others from using their original works of expression without permission.
Trade secrets (Know-How): Information, processes, techniques, designs, or other knowledge not generally made public, which provide the holder with a competitive advantage in the marketplace.
Database Rights: Protection for the compilation of critical data for up to 15 years.
Design Patents: Design Patents which cover the design aspects of products to differentiate them from others.
For medical devices, the most important aspect of IP is Patents. The patentability requirements mandate that the subject matter of the claimed invention be: (i) patent eligible, (ii) useful, (iii) new, (iv) non-obvious, and (v) described with the particularity required so that people of skill in the relevant technology field or science can understand what the invention is, make the invention, and use the invention without engaging in what the law calls undue experimentation.

Who owns the IP and how much will it cost?

Inventors working in an academic setting must keep in mind that if an invention is conceived and/or developed using significant university resources, the university may assert its rights in taking ownership of the invention. The same applies to an inventor working in a commercial or healthcare setting. The employer may assert its rights in the ownership of the invention depending on the contracts in place between the inventor and the employer.
There are several costs associated with patents. An IP attorney/law firm will be reviewing your patent and filing patent applications across different geographies. The costs include basic filing fees for each country, and maintenance fees upon acceptance.

What do I need to do before I apply?

Freedom to operate search: A new device has freedom to operate (FTO) only if the features of the device are free and clear of valid claims from patents that are still in force in the country in question. If there are features in the prior claim that are not part of the new invention, then FTO is preserved.

The Prior Art Search: Understanding prior art landscape for a new invention is one of the most important parts of innovation. If the search reveals troublesome prior art, you shall benefit greatly from finding this information as quickly as possible. Such discoveries can potentially save you huge amounts of wasted time and resources in pursuing the wrong idea. The invention can also be modified into an approach that is patentable.

Where to look?

PatSnap; Google Patent Search; U.S. Patent and Trademark Office's, Patent Full-Text.
International Patents Databases: **WIPO Patent Scope**; **The European Patent Register Online**.

What are the different routes to file for patents?

Local Patenting: If you are seeking protection in only a few countries, it may be best to apply direct for a patent to each of the national offices. Patents must be filed in each country where patent protection is desired, and could be a costly and resource heavy approach.

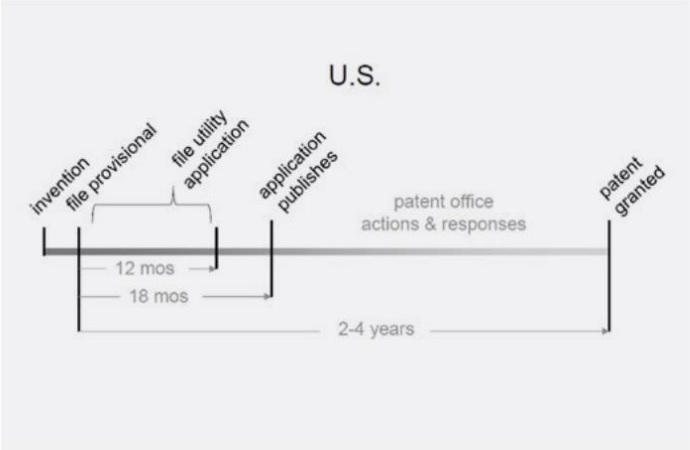
International Patenting:

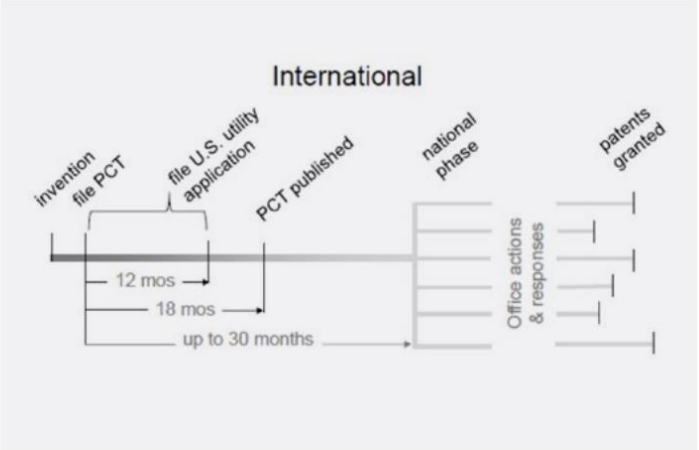
US: A Provisional Patent can be filed with initial description of an invention that establishes a priority date before filing the utility patent in the US. Upon application of a provisional patent, a non-provisional (utility) patent has to be filed within 12 months. The timing for a US patent filing is shown below. It is important to note that the provisional patent is never published, so after filing it is possible to work on the new invention in complete secrecy.

It is only after a US utility patent application is filed claiming priority to the provisional application that the invention will ultimately be published (18 months after the provisional filing date). Find further information and guidance at the USPTO office website.

EU, USA, others: The European Patent Office accepts applications under the European Patent Convention (EPC) and the Patent Cooperation Treaty (PCT). The information regarding applying for patent in the EU is mentioned HERE. The attorney or law firm and the EPO will guide you with the application procedure. Under the PCT, a single filing of an international application (called a PCT) is made with a Receiving Office in a single language (the receiving offices are typically the patent offices of the PCT contracting states). There is no collective "international patent" that results from PCT process—patents must be reviewed and granted individually by patent agencies in each of the countries in which coverage is sought. The PCT provides is a way of starting the application process in an efficient and relatively economical way (i.e., a few thousand dollars) and receiving a preliminary opinion on patentability from an expert international agency (International Searching Authority).

Other Countries: Patenting in each country is managed by their respective national patent offices. The details can be found on the WIPO portal.





MEDICAL DEVICE CLASSIFICATION

Medical device innovators should determine their device classification from the outset, as it will inform the correct regulatory pathway per market and also determine requirements for the product development phases.

What regulations apply?

- In the EU, device classification is dealt with in Annex VIII of Regulations EU MDR 2017/745 (Medical Devices) and EU IVDR 2017/746 (In Vitro Diagnostics). Updates and publications can be found HERE.
- In the USA, medical device and radiation-emitting product regulations are in the Code of Federal Regulations Title 21 CFR Parts 800-1299, which covers various aspects of design, clinical evaluation, manufacturing, packaging, labelling and post market surveillance.

Who owns the IP and how much will it cost?

Inventors working in an academic setting must keep in mind that if an invention is conceived and/or developed using significant university resources, the university may assert its rights in taking ownership of the invention. The same applies to an inventor working in a commercial or healthcare setting. The employer may assert its rights in the ownership of the invention depending on the contracts in place between the inventor and the employer.

There are several costs associated with patents. An IP attorney/law firm will be reviewing your patent and filing patent applications across different geographies. The costs include basic filing fees for each country, and maintenance fees upon acceptance.

What are 'Intended Use' and 'Indication for Use'?

Irrespective of different classification systems in force per country or region (EU), devices are generally 'classed' according to their intended purpose and the inherent risks they pose to patients and users. Before determining device classification, you should articulate the 'Intended Use' and 'Indications for Use' for your device. This also allows defining user needs, design inputs, and other design and development activities. Intended Use is the general purpose of the medical device or its function, i.e., what you "claim" the medical device does. Indications for Use describe the disease or condition the medical device will diagnose, treat, prevent, cure, or mitigate, including a description of the target patient population. Refer Article 2 – Definitions, of **EU MDR 2017/745 (Medical Devices)** for aspects to consider regarding Intended Use.

How are devices classified in the EU?

Medical device classification is rules-based and simple to follow: There are 22 rules that guide your device's classification (Annex VIII of EU MDR 2017/745), which are each to be considered alongside the device's duration for use.

Chapter V Section 1 Article 51 of EU MDR 2017/745 details the four main categories for medical device classification. (Article 52 deals with conformity assessment).

- Class I (lowest risk)
    - Class Is: Class I product delivered sterile;
    - Class Im: Class I product with a measuring function
    - Class Ir: Class I products that are reprocessed
- Class IIa
- Class IIb
- Class III (highest risk)

For Classes Is/Im/Ir/II/III a notified body is required for certification of the specific sub-class aspect.

For in-vitro diagnostic devices a 7-rules system applies. Chapter V Section 1 Article 47 of EU IVDR 2017/746 outlines the in vitro device classification. (Article 48 deals with conformity assessment).

- Class A (lowest risk)
- Class B
- Class C
- Class D (highest risk)

Classes B/C/D will require assessment and certification by a notified body for medical devices (appropriately designated for IVDs).

If your software is intended to be used for one or more medical purposes and performs these without being part of a hardware medical device, it is most likely Medical Device Software (MDSW) or In Vitro Diagnostic Software (IVDSW). The Medical Device Coordination Group published a good resource to help with classification. Take note of 'special cases', if applicable, such as: combination products, medical devices with an ancillary medicinal substance, companion diagnostics, medical devices made of substances that are systemically absorbed, and borderline products (Medical Device Borderline Manual of the EU Commission).

How are devices classified in the US?

The process of determining device classification for the USA market involves a different approach versus the EU, but the FDA provides clear instructions including a useful video. Classification is directly related to the Intended Use and Indications for Use of the device. The FDA has established classifications for approximately 1,700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. All devices within the database are assigned to one of three regulatory classes based on the level of 'control' necessary to assure the safety and effectiveness of the device. Therefore, you can look for devices similar to yours and determine its classification this way. Also, you will be able to determine the regulatory control requirements for your device. 'General Controls' apply to all medical devices (unless exempted by regulations), 'Special Controls' are added for Class II devices, and Class III devices require General Controls and Pre-market Approval (PMA). The three classes and the requirements which apply to them are:

- Class I (low to moderate risk)
  General Controls
  – With Exemptions
  – Without Exemptions
- Class II (moderate to high risk)
  General Controls and Special Controls
  – With Exemptions
  – Without Exemptions
- Class III (high risk)
  General Controls and Premarket Approval

What is a Regulatory Pathway?

Once you have decided your device classification per the EU and/or US, you will know what your 'pathway' to market is:

EU: Your device's classification determines the conformity assessment requirements. Therefore, depending on the device classification, one of the following would apply:

- Self-declare & registration: Typical for Class I: nonsterile, non-measuring, non-reprocessed
- 3rd party audit (by an accredited notified body organisation):
    - Class Is/Im/Ir: Sterility / measurement / reusability.
    - Class IIa/IIb/III: ISO13485 QMS & Technical documentation (safety & performance data; clinical data to support safety & efficacy).

USA: Broadly speaking your path to market is most commonly one of:

- Class I/II exempted products: Many Class I and certain Class II devices are exempt from the premarket notification (PMN) and/or the quality system (QS) regulation.
- Class I/II non-exempted products: Generally, a premarketing notification (PMN), known as a 510(K) is used for moderate-risk devices not exempted from pre-market review. Substantial equivalence with a predicate device must be shown; either a previously cleared Class I/II device not requiring a pre-market approval (PMA), or a pre-amendment Class III for which the FDA has not issued regulations requiring a PMA. Because novel devices lacking a legally marketed predicate are automatically designated Class III, the FDA introduced the De Novo route, an expedited mechanism for reclassifying these devices based on risk. Although requiring more data than a traditional 510(k), DE Novo often requires less information than a PMA application.
- Class III PMA: This is a stringent route for new or high-risk devices that require some clinical data before an approval decision.

MEDICAL DEVICES REIMBURSEMENT: AN INTRODUCTION

Medical device innovators should understand the importance of reimbursement and that it should be dealt with early. Also, become familiar with ‘valuebased’ healthcare and health technology assessment (HTA).

What is reimbursement?

Reimbursement, in the context of medical devices, is the payment by a public or private insurer or ‘payer’ to a health care provider for the costs the provider incurred in using a medical device or in performing a procedure. If a device is reimbursed it is said to be ‘covered’. Reimbursement mechanisms constitute mainly three constituents.

- Coverage criteria: The payers’ motivation or willingness to pay for a certain device or procedure.
- Device or procedure ‘code’: An alphanumeric symbol, used to identify the device and/or procedure in order to facilitate smooth communication between payers and healthcare providers.
- Payment rate: The amount that will be paid by payers following the use of the covered device.

A ‘fourth’ constituent is the ‘care setting’, as reimbursement mechanisms are setting-specific. For example, a device such as a blood pressure monitor could be used in a hospital inpatient setting, in an ambulatory setting (e.g. physician’s office), or even in the patient’s home. And depending on the setting where the device is used, different coverage criteria will apply, different codes will be reported, and different payment rates will be assigned.
HERE is a useful article entitled “What is Healthcare Reimbursement? Definition, Models and Resources”.

Why should I think about reimbursement now?

A healthcare provider’s ability to offer new technologies depends on whether the new medical device can be covered as reimbursable or not, and what that coverage amount is. This in turn affects a device manufacturer’s ability or willingness to provide the device. There is an increasing burden for medical device innovators to provide insurers and healthcare providers with evidence of clinical and economic effectiveness to inform a coverage decision, and consequently innovators may be deterred from the sheer cost and effort of developing and bringing new technologies to market.

In today’s world medical device companies need to start engagements with payers and providers early on in the product development process, and indeed often must lead the reimbursement process to increase the chance of product acceptance and coverage. To underline this point, investors have reimbursement at the top of their list when considering investment opportunities, therefore it should be one of the first things innovators think about when developing new products.

Where do I start?

The first step in planning for reimbursement is to identify the setting/s in which your device will be used. Then you can determine if your device fits within an existing reimbursement mechanism (code, coverage and payment rate), and if so, reimbursement is theoretically immediately possible. Alternatively, you will need to embark on the process of developing new reimbursement mechanisms (new code, new coverage criteria, and/or a new payment rate). This requires presentation of specific clinical data to prove the clinical and economic benefits of your device, and you will need to establish

an initial user base per country and harness the support of the local medical community. This process could take years and is costly. Alternatively, innovators may instead choose to modify their device features, functionality or specifications in order to instead fit under existing reimbursement mechanisms. In the latter category, it is easy to see why early reimbursement planning is critical: If a device company leaves reimbursement planning until after product design and/or clinical trials there is a risk either or both may have to be repeated if its product does not satisfy existing reimbursement codes, coverage and payment rates it was planning to use. This will lead to additional costs, delays to commercialisation and a reduced return on investment.

What are other important things to consider?

Code ≠ reimbursement: In order for a device to be reimbursed, the relevant decision-makers (typically payers) must first decide whether they will cover the device and if so, how much they will pay for it. To complicate matters, new devices seldom achieve national reimbursement from the start. Often the device company may have to start at the level of an individual hospital that may have a budget to acquire certain technologies or serve certain patient cohorts. Or certain payers or charity funds may allocate a portion of their budget to new technologies for the benefit of their members. It is most-times a long and arduous journey for manufacturers to establish their initial user base and gather real-life health economic and clinical evidence before convincing other providers and payers. The importance of early discussions with providers and payers cannot be overstated.

Decision makers: If your device can utilise existing reimbursement mechanisms payers do not have to be involved. Physicians and hospital management become your main decision makers, but you must be able to provide compelling evidence of the clinical and economic benefits of your device versus the currently available alternatives. Hospitals or physicians can then purchase your device and bill for it under existing reimbursement mechanisms. Conversely, if new reimbursement mechanisms need to be developed, payers will have to be convinced of the clinical and economic benefits of covering the use of your device before they agree to develop the required reimbursement mechanisms. It's important to realise that provider and payer decision makers will view clinical and economic benefits from their own organisational standpoint, therefore clinical studies and economic models should be designed with the main decision maker in mind.

Think global, act local: Developing new reimbursement mechanisms is almost impossible without harnessing the support of the local medical community and developing an initial user base. In addition to your KOLs, initiate a two-way engagement with local medical societies and advocacy groups as their support when applying for new codes will be helpful. In terms of an initial user base, some countries have formal national programs to encourage the introduction of innovative medical devices prior to reimbursement. In other countries regional hospital grants (e.g., Italy and Spain) or even support from charity funds (e.g., the UK) may be utilised to help with establishing this initial user base. Recently, a new "Innovation Fund", which provides funding for particular projects, was established in Germany, which may also be used to generate required evidence and help in establishing an initial user base.

The EU is diverse - are some EU countries more attractive than others?

Each EU country maintains its own reimbursement mechanisms, and so reimbursement in one EU country does not imply reimbursement in another. Criteria to consider when choosing the initial country markets might be market size (health expenditure) and ease of the reimbursement process. In this way, manufacturers might typically start with Germany and the UK as their first markets, followed by France, Italy and Spain as the second tier. Alternatively, you may be working with a healthcare provider or clinical collaborators in a particular EU country and may therefore choose this as your beachhead market based on relationships and traction you have already established.

How is the US healthcare reimbursement system structured?

The has a decentralised system that features a large number of payer decision-makers:

- 1500+ commercial health insurance plans.
- 12 Medicare local contractors and one Medicare central office for elderly and disabled.
- 50+ Medicaid agencies for the poor/indigent.
- Managed Care: Integrated Delivery Networks (Kaiser), Accountable Care Orgs (ACOs).
- Military: Veterans Affairs, Tricare.

Reimbursement depends on the setting of care and benefit category, and each care setting has its own system for payment. Care settings are hospital inpatient, hospital outpatient, physicians services, and retail pharmacy.

What is Medicare and Medicaid?

Medicare: Medicare is the largest payer in the US. While it originally covered only those aged 65 or older, independent of income and medical history, it has now expanded to include citizens with permanent disabilities and end-stage renal disease in those aged under 65.

Medicaid: Medicaid is a health coverage program that provides care to people that cannot afford their own medical expenses. It is available to low-income individuals or families that fulfil certain criteria. Amongst the health services Medicaid covers are hospital stays/visits, doctor or emergency room visits, prescription drugs, and others.

To give context to the importance of Medicare and Medicaid in the US reimbursement landscape, the health insurance coverage breakdown of the US population is: Commercial insurers 55%, Medicaid 20%, Medicare 14%, 'Uninsured' 9% and Military <2%.

Where can I find resources for reimbursement in the EU?

Each EU country has its own pricing and reimbursement strategy, links for certain countries are below:

Germany: All medical treatment provided under the statutory health insurance system must be approved (either implicitly or explicitly) by the federal joint committee (Gemeinsamer Bundesausschuss – G-BA). Different systems operate for the inpatient and outpatient sectors. Details of the 2020 G-DRG system are available on the InEK website at: www.g-drg.de/G-DRG-System_2020

France: Devices that are endorsed by the Commission nationale d'évaluation des dispositifs médicaux et des technologies de santé (CNEDiMTS) in terms of their clinical value must also be reviewed by the healthcare products pricing committee (Comité économique des produits de santé - CEPS). The CEPS is charged with setting official prices and reimbursement levels. The list of reference prices is known as the Tarif forfaitaire de responsabilité (TFR). The CEPS also sets prices of an additional list of hospital products outside the fee-for-service payment scheme. There are two methods of reimbursement of medical devices in France:

- Medical devices integrated into homogenous groups (Groupe Homogène de Séjour, GHS) in health establishments (DRG); and
- Medical devices included on the Liste des Produits et Prestations Remboursables (LPPR).

Spain: The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS, or Spanish agency for medicines and health products) operates as an autonomous body under the Ministerio de Sanidad, Servicios Sociales e Igualdad (MSSSI, or Ministry of Health). Hospitals use a DRG-system to record activity rather than fund hospital care. Therefore, hospital care is paid for on a budget-based system. In order to gain reimbursement, products must provide value for money, so the use of health technology assessment (HTA) is common.

Italy: There are three main national competent authorities. However, pricing & reimbursement must be negotiated at a regional rather than national level, with three major regional or hospital bodies. The reimbursement rates are defined in three tariffs at national level, in order to ensure a uniform approach is adopted among the regions: • Nomenclatore tariffario dell'assistenza specialistica ambulatoriale – nomenclature tariff of specialist ambulatory care; • Nomenclatore tariffario protesi – nomenclature tariff for prostheses; and • Tariffe delle prestazioni di assistenza ospedaliera per acuti (sistema DRG) – tariff of care in acute hospitals under the diagnosis related group (DRG) system.

Netherlands: Reimbursement policy is developed by the Ministry of Health, Welfare and Sport, in conjunction with the National Healthcare Institute (Zorginstituut Nederland – ZiN) which is responsible for overseeing the benefits provided for under the basic health insurance package and advising the Health Minister on the reimbursement of new therapies and technologies and changes to the existing reimbursement schedule.

Denmark: There is no specific price setting mechanism in place for medical devices, but prices are influenced by degrees of reimbursement and/or public tenders. The Danish Medicines Agency (DKMA) is responsible for reimbursement decisions for both medicines and medical devices. Depending on the medical device, the reimbursement level is either fixed (e.g. at 100%) or variable according to the local authority decision. Denmark has developed a modified regional diagnosis related groups system (DkDRG) which has been used since 2012. This is based on the regional NordDRG, which was developed using definitions from ICD-10. The cost of many medical devices used in hospital procedures is included within the DRG tariff. Additionally, there has traditionally been an ambulatory group system (DAGS) for outpatient care. The DkDRG system is updated on an annual basis by the Danish Health Data Agency (SDS - Sundhedsdatastyrelsen).

What are the resources for reimbursement in the UK?

Pricing of medical devices and equipment in the UK is not directly regulated. To make the NHS more efficient, the UK government has put in place a Payment by Results (PbR) system. Under the PbR system, healthcare providers are paid for each patient seen or treated, taking into account the complexity of the patient's healthcare needs. The tariff received by the provider is adjusted to reflect the nationally determined market forces factor (MFF), which is unique to each provider. NHS England will fast-track the introduction of selected innovative medical devices through the Innovation and Technology Tariff (ITT) program.