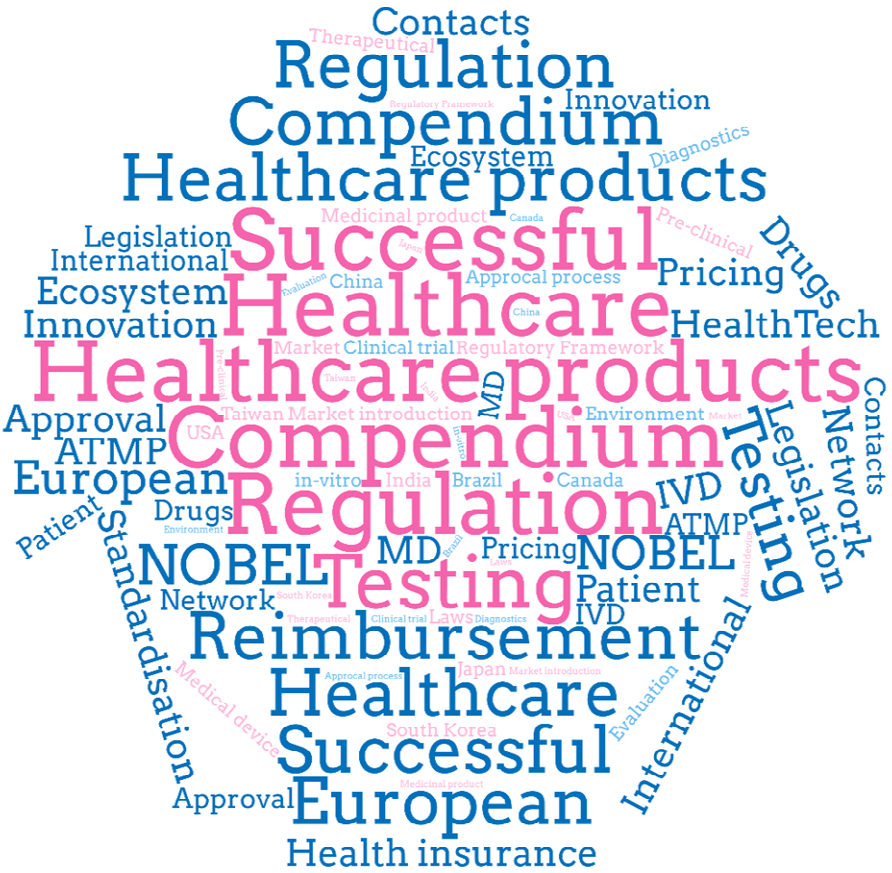

Testing, regulation and reimbursement of healthcare products

- *A compendium for successful translation* -

NOBEL
Smarter HealthTech in Europe

www.nobel-project.eu

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Introduction – the Ecosystem of Healthcare products

The translation of any new medical invention, including nanomedicine, into a final product is a highly regulated and complex process. The process can be roughly divided into a pre-clinical and clinical trials part - governed by regulation agencies such as the European Medicines Agency (EMA) or National Agencies - and in continuation, into a part dealing with pricing and reimbursement issues, which are mainly handled by national or regional authorities.
This compendium gives a broad overview of this regulatory ecosystem and issues to be considered on the way from research proof of concept to the patient. It can be used as kind of a guidance listing the requirements and processes for the three main areas: preclinical and clinical regulations plus reimbursement.
Two main procedures can be distinguished: one for **medicinal** (pharmaceutical) **products** and one for **medical devices** and **in vitro diagnostic products.** Medicinal products require extensive pre-clinical validation followed by three clinical phases, which takes several years and requires large financial resources. In comparison, medical devices and in vitro diagnostic products are audited by Notified Bodies with regard to functionality and safety and, depending on the risk classification, also require clinical trials. Therefore, assignment of an invention to one or the other system is critical. However, this assignment can be different in Europe or other parts of the world, especially for so-called borderline products, which combine a diagnostic and therapeutic feature. Early contact to the relevant regulators described below is recommended to take this decision.

Regulation of Medicinal Products[1]

Medicinal products are defined in the European **Directive 2001/83/EC** on Medicinal Products for human use as:

a) Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; or
b) Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis.

In general, new (nano)medicinal products in Europe have to pass through the following steps to finally reach the patient:

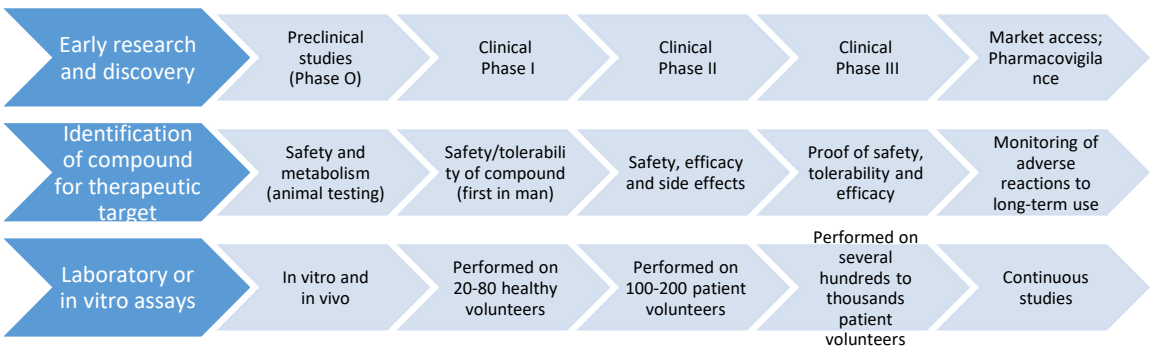


Figure 1: Overview of the regulatory process for medicinal products

The whole process takes about 10 to 15 years and involves many different authorities at EU and national level.
To obtain a market authorisation for a new product, pre-clinical and clinical data have to be sent to either the European Medicines Agency (EMA)[2] in a centralised procedure to achieve authorisation for whole Europe or to a National Agency in a Member State to receive authorisation for this Member State. To expand the authorisation to other Member States in Europe,

[1] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf
[2] http://www.ema.europa.eu/ema/

the application can be sent simultaneously to other Member States (Decentralised Procedure), or the existing authorisation of the first Member State is accepted by other states (Mutual Recognition Procedure).

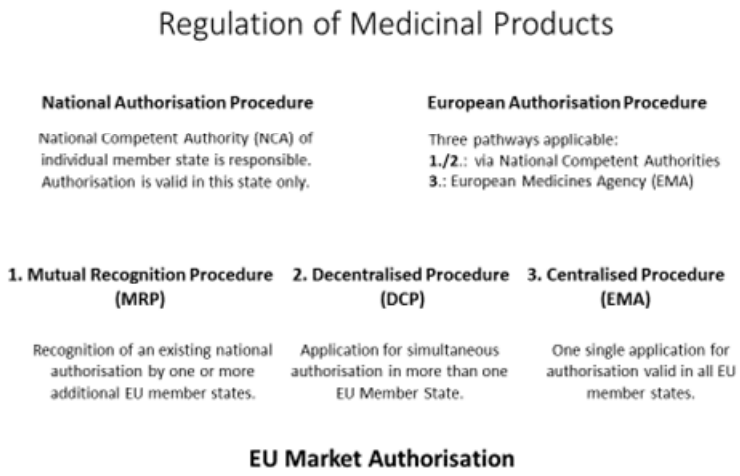


Figure 2: Alternative market authorisation procedures in Europe

The relationships of all three procedures are illustrated in figure 2 and are described in a small booklet published by EMA[3]. In addition, EMA publishes the SME OFFICE NEWSLETTER[4] which provides helpful information for SMEs in the EU regulatory environment for medicines.

The centralised procedure is mandatory for the following diseases and products:

- AIDS, cancer, diabetes
- Neurodegenerative diseases
- Advanced therapy medicinal products
- Medicinal products derived from biotechnology processes such as genetic engineering
- Orphan medicines

An option exists of submitting an application for medicines:

- that stand for a significant therapeutic, scientific or technical innovation
- whose authorisation would be in the interest of public or animal health

In case of a positive decision, the European Commission or Member State grants market authorisation, and a European Public Assessment Report (EPAR) describing some features of the new medicinal product is published on the EMA homepage.
It is recommended to contact a National Agency[5] or the European Medicines Agency (EMA) as early as possible to discuss the requirements to be fulfilled to obtain their approval. Both provide customised advice sessions for applicants, which are subject to fee. At EMA, SMEs can apply for special reduction of fees[6] for scientific advice. In addition, EMA has an Innovation Task Force[7], which is happy to learn and to discuss about general very new nanotechnological and biomaterial developments, for example.

[3] https://www.ema.europa.eu/en/documents/leaflet/european-regulatory-system-medicines-european-medicines-agency-consistent-approach-medicines_en.pdf
[4] https://www.ema.europa.eu/en/documents/newsletter/news-bulletin-small-medium-sized-enterprises-issue-48_en.pdf
[5] https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
[6] https://www.ema.europa.eu/en/human-regulatory/overview/supporting-smes
[7] https://www.ema.europa.eu/en/documents/leaflet/innovation-task-force_en.pdf

To cover the cost for the long and expensive regulatory process a number of different European sources of financing for SMEs exist[8]. An overview of support provided to medicines developers by EMA is available. In addition, EMA published a User guide for micro, small and medium-sized enterprises[9].

Pre-clinical evaluation

The first task to get authorisation to put a new (nano-)medicine on the market is to prove its safety. For this purpose, the new product has to be characterised in a so-called pre-clinical phase by several physicochemical and toxicological test systems. In this phase the homogeneity of a product with regard to batch to batch consistency and presence of production impurities is analysed. In addition, geno-, cyto- and immunotoxicity are investigated in in-vitro and in-vivo (small animal) models. Once these data have been confirmed by a Contract Research Organisation (CRO) they have to be presented in a dossier to the Competent Authority in the Member State(s) where the clinical trial(s) will be performed.

Clinical trial evaluation

Once the European Commission or the Member State(s) have accepted the data of the pre-clinical evaluation a new product can enter clinical trials. Clinical trials assess the effectiveness and safety of medicines by checking their effects on humans.
Currently, all clinical trials carried out in the EU are performed in accordance with the **Clinical Trials Directive 2001/20/EC**[10].
Clinical trial sponsors have to go through a dual submission procedure in each Member State where clinical trials will be performed. The documents have to be submitted to the National Competent Authority and in parallel to the national Ethics Committee[11] for evaluation according to the ethics principles of the Helsinki Declaration[12]. To obtain an overview of National Competent Authorities for Clinical Trials, please consult **EudraCT[13].** An overview which Ethics Committee needs to be contacted in the different Member States is provided by the **European Network of Research Ethics Committees**[14]. The EU Clinical Trials Register[15], launched by EMA in March 2011, allows public access and search for information on completed and ongoing clinical trials for medicines.
The data have to be sent in the **ICH-GCP** format, which serves as the basis for an adequate documentation. **ICH** (International Conference on Harmonisation = international bodies from America, Europe and Japan) **- GCP** (Good Clinical Practice) represents an international quality standard for a set of criteria such as conduct monitoring, auditing and reporting of clinical trials. It ensures that the data and the results are reliable and accurate, and that confidentiality and rights of subjects and volunteers are protected.
Since the whole process and the documentation requirements are very complex and need special expertise, it is recommended to authorise a **Contract Research Organisation (CRO)** with the professional management of the complete clinical trials procedure. A CRO provides full support in pre-clinical and clinical trials management and pharmacovigilance by offering to their clients the expert knowledge of transferring a new (nano)pharmaceutical from its concept to market approval. **EUCROF**[16], the European CRO Federation with members and associate members in 23 countries, represents 350 member CROs in the EU. Amongst other objectives, it develops training and educational programs for clinical research and assists the national member associations in setting up such programs.
To make this multistate application process easier and to harmonise the conditions and requirements in Europe, the EU Council and the EU Parliament have negotiated and agreed on a new Clinical Trials Regulation EU No 536/2014[17] (EU-CTR) which was supposed to become applicable in October 2018 to replace the current Clinical Trials Directive no 2001/20/EC. However, to come into force the EU-CTR depends on a fully functional **Clinical Trials Information System[18]** (**CTIS**, formerly

[8] https://www.ema.europa.eu/en/documents/other/tools-available-micro-small-medium-sized-enterprises-smes_en.pdf
[9] https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/user-guide-micro-small-medium-sized-enterprises_en.pdf
[10] http://ec.europa.eu/health/files/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf
[11] https://www.coe.int/t/dg3/healthbioethic/cometh/national_ethics_committees/
[12] https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[13] https://eudract.ema.europa.eu/nca_contacts.html
[14] http://www.eurecnet.org/information/index.html
[15] https://www.clinicaltrialsregister.eu/about.html
[16] https://www.eucrof.eu/members/directory
[17] https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-1/reg_2014_536/reg_2014_536_en.pdf
[18] https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials/clinical-trial-regulation

the EU clinical trial portal and database), which is scheduled to be operational in 2020. Due to this delay the old directive is still operational and will be applicable most likely until October 2021. (EU portal and EU database delivery time frame[19]).

The main characteristics of the new regulation are:

- Registration via a single EU entry portal for all clinical trials conducted in Europe,
- Harmonised authorisation procedure with a single set of documents and a central database for all clinical trials,
- Authorisation procedures carried out by National Competent Authorities in the Member States according to common protocols.

In contrast to the previous Clinical Trial Directive (EU-CTD), where the sponsor of a clinical trial had to apply in each targeted Member State separately with partly different requirements, the new Clinical Trial Regulation (EU-CTR) now arranges for the application to be sent to a central EU-Portal located at EMA, which serves as the single entry point for the submission of all data and information relating to clinical trials.

In order to obtain an authorisation the sponsor will submit, via the EU-portal, a single application dossier to all Concerned Member States (CMS) where it is intended to conduct the trial. Among the CMS the sponsor can appoint a Reporting Member State (RMS), which coordinates all evaluations and functions as the single communication point with the sponsor.
Using a harmonised format, the application dossier will consist of two parts:

- Part I deals with scientific and technical issues of the trial.
- Part II deals with national regulations concerning patient informed consent, ethical issues, investigators and facilities suitability or data protection issues.

This later part requires Member State specific data to be submitted through the portal and handled by the national Competent Authorities and Ethics Boards. An Overview of the authorisation procedure and the timeframes for evaluation under EU-CTR is shown in figure 3.

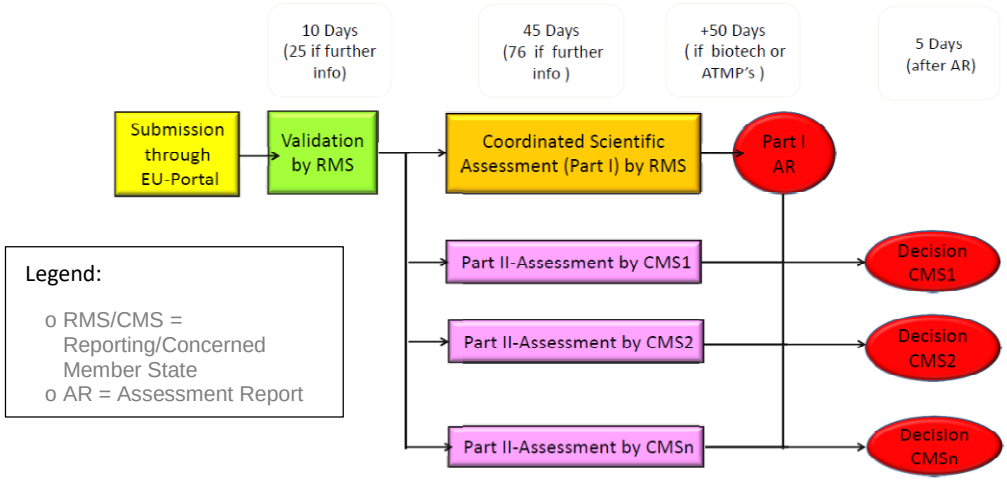


Figure 3: Summary of clinical authorisation procedure under EU-CTR[20]

At the end of the clinical validation process EMA or a Member State will grant the authorisation to put the new product on the healthcare market. However, since the market is highly regulated as well, the sponsor needs to go through the reimbursement validation process to set the price and market channel to the patient.

[19] https://www.ema.europa.eu/en/documents/other/delivery-time-frame-eu-portal-eu-database_en.pdf

[20] Source: V. Debaut (2015) - The EU Clinical Trials Regulation – Main Changes and Challenges. Published as a White Paper by CROMSOURCE. https://www.cromsource.com/wp-content/uploads/2015/02/The-EU-Clinical-Trials-Regulation-Main-Changes-and-Challenges.pdf

Pricing and Reimbursement

As explained above going through the regulatory process up to the market authorisation is a time-consuming and expensive procedure. To get a return on this investment the producer of a new (nano)medicine needs to obtain a price for his product high enough to cover the costs.
If the product does not need a prescription but can be sold freely over the counter (OtC), the price can be fixed freely by the producer. However, if it is a prescription medicine the price for the product cannot be set freely by the sponsor but is subject to a complex pricing and reimbursement process with national or even regional authorities and health insurances based on criteria such as efficacy or innovation potential in comparison to existing products.

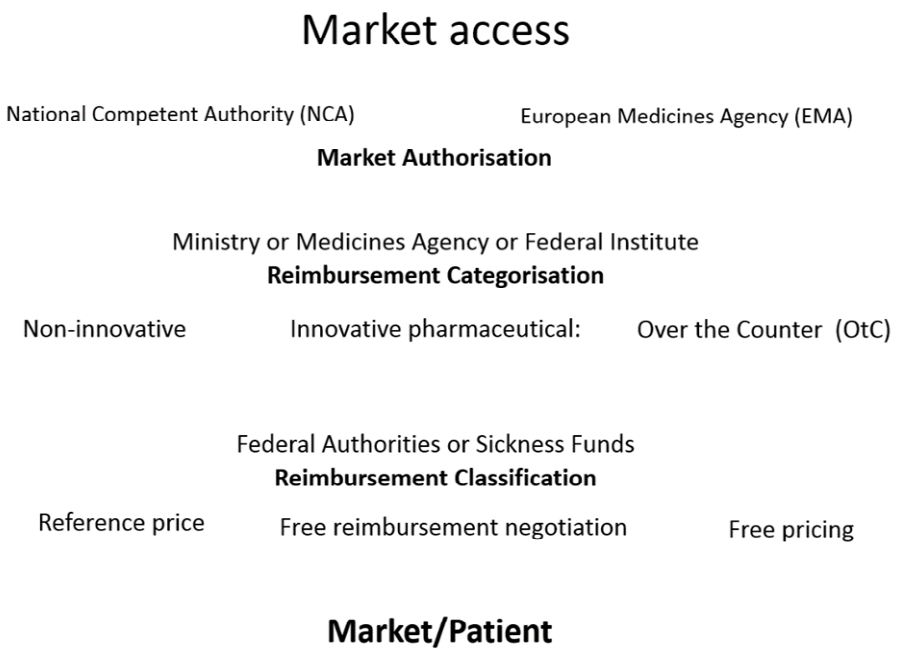


Figure 4: Reimbursement processes

As pricing and reimbursement of **medicinal products** (pharmaceuticals) are subject to the individual responsibility of each Member State, various systems exist at present within the European Union. The entry portal for application for reimbursement of medicinal products are ministries or healthcare agencies or insurances, which ask expert teams to categorise the product according to the criteria mentioned above. A list of responsible ministries and agencies is provided in Annex 1.
The national price setting processes start with a Europe-wide price comparison with similar pharmaceuticals. The comparison involves economic viewpoints, pharmacological tests, the assessment of a therapeutic benefit and a health technology assessment (HTA).
If the new product compares to a large extent with an existing product, it is regarded as non-innovative, and the price is fixed at the same level of the comparable product. In case the product is regarded as innovative the producer can start price negotiations with the responsible ministry or health agency.
Due to cost constrains in all European healthcare systems, authorities are interested to lower the price as much as possible. This can lead to the situation that a product will not achieve the price necessary to gain the return on investment needed. Therefore, producers should check as early as possible with reimbursement agencies the criteria applied to the price setting for their particular product to decide, if the product is profitable enough.

Regulation of Medical Devices (MD) and in vitro Diagnostic Medical Devices (IVD)

As stated in the beginning, the regulatory process to get market approval for medical devices (MD) and in vitro Diagnostic Devices (IVD) are different and were based until 26th May 2020 on the Medical Devices Directive 93/42/EEC[21] (MDD) and Directive 98/79/EC for IVD[22]. In 2012 the **European Commission started to revise both directives**. The resulting **Medical Device Regulation (MDR)** and the **in vitro Diagnostic Devices Regulation (IVDR)** were officially published on May 5th 2017 and entered into force on May 25th 2017. The MDR (EU) 2017/745 replaces EU current Medical Device Directive (MDD 93/42/EEC) and EU Directive on active implantable medical devices (AIMDD 90/385/EEC). The IVD (98/79/EG) does not merge into MDR but has been replaced by an own regulation: (EU)2017/746. As these are regulations and not directives, they require no particular transformation into national law.
Both regulations substantially change the previous process and make it more demanding and time and resource consuming. The biggest changes are:

- Notified Bodies lose their status. They will have to be audited again which already caused strong delays
- The technical documentation needs to be much more detailed
- More products will require clinical trials which also need to be updated by post market monitoring
- Additional oversight of the complete supply chain including importers and distributors. To achieve this, a central data bank for medical products (EUDAMED) will be introduced and a Unique Device Identification (UDI) number will be implemented which has to be put on each MD. As UDI data bank has not been introduced yet and EUDAMED specifications still have to be defined by the EU, a practical realisation of these regulations will take time
- Unannounced audits by Notified Bodies in post market surveillance
- Manufacturers need an authorised representative knowledgeable and responsible for regulatory compliance ensuring the declaration of conformity, performance evaluations and vigilance requirements are kept up-to-date.

It is expected that 80 – 90% of all IVDs will require regulatory review by Notified Bodies in contrast to the previous 20%. The transition phase for issuing certifications according to MDR will end on 26th May 2020, for the IVDR it will last five years until 26th May 2022.

In the new MDR the following main definitions apply:
'medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. The following products shall also be deemed to be medical devices:

- devices for the control or support of conception;
- products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.

For the IVD Regulation, the following main definitions apply:

- **'medical device'** means 'medical device' as defined in point (1) of Article 2 of MD Regulation (EU) 2017/745;

[21] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:en:PDF, p.7
[22] http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31998L0079

- **'in vitro diagnostic medical device'** means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:
    a) concerning a physiological or pathological process or state;
    b) concerning congenital physical or mental impairments;
    c) concerning the predisposition to a medical condition or a disease;
    d) to determine the safety and compatibility with potential recipients;
    e) to predict treatment response or reactions;
    f) to define or monitoring therapeutic measures.

For the purposes of this Regulation, the following definitions apply:

- Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;
    a) 'specimen receptacle' means a device, whether of a vacuum-type or not, specifically intended by its manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination;

To get market approval the regulatory process is as follows:

1. • **Selection of relevant EU Regulation (new)** ***or Directive (old)*****:** Regulation (EU) 2017/745 on Medical Devices (MDR); Regulation (EU) 2017/746 on In-Vitro Diagnostic Devices (IVDR)
2. • **Classification:** Class I, IIa, IIb, III for Medical Device or A, B, C, D for In-Vitro Diagnostic Device
3. •**Introduction of Quality Management System (QMS)** according to e.g.: ISO 13485 standard. Class I products (non-sterile, non measuring) do not need a QMS but a PMS (Performance Management System) which is not audited by a Notified Body.
4. • **Preparation of Technical File** (Classes I-IIb) providing clinical data **or Design Dossier** (Class III/AIMD). Clinical studies are needed for class IIb, III and implants. Existing clinical data may be accepted.
5. • **Appointment of Authorized Representative (EC Rep)** to handle regulatory process on behalf of a company which is not located in Europe
6. •**Audit of QMS and Technical File** (except class I, non-sterile, non measuring) **or Design Dossier by Notified Body.** If successfully completed, CE certificate will be issued (Validity: 3 years) and an ISO 13485 certificate for the facility (to be renewed every year).
7. • **Presentation of Declaration of Conformity** stating the device is in compliance with relevant regulation or directive. CE-Marking may now be attached.
8. • **Registration of class I devices with Competent Authority** of your company
9. • **Annual audit of Medical Devices of all classes except class I** (non-sterile, non measuring) **by a Notified Body** to prove continuous compliance with regulation or directive.

Figure 5: Regulatory process for medical devices

The final goal of the process is to get a **CE mark** for the product, which proves the safety of the product its compliance with the standards listed in the regulations.

It is obvious that depending on the risk classification of a product the requirements to prove the safety differ significantly.
The **second important requirement**, besides risk classification, **is the introduction of a Quality Management System (QMS)** by the manufacturer according to the standards of the regulations. This provides the basis for the technical file or design dossier, which is audited by a Notified Body.

A **Notified Body** is an organisation that has been accredited by a Member State. It assesses medical devices whether they conform to fixed standards in the EU regulations. Assessment includes inspection and examination of function and safety of a product, its design and manufacture processes and conditions.

Based on the audit of the Notified Body, the EU Member State will inform the European Commission whether a product complies with standards or not. With a Declaration of Conformity, the manufacturer is entitled to label the product with the CE Mark which is required for distribution and sale in the EU.
Manufacturers may individually choose a Notified Body within the EU[23] insofar as it is accredited for the execution of the relevant conformity assessment procedure.

Pricing and Reimbursement

As for medical products, the rules for **reimbursement** of medical devices within the European Union vary from one Member State to the other (see Annex 2). In most states Health Technology Assessment (HTA) agencies[24] were set-up to decide which product will be formally approved for use in a medical procedure ensuring that only those medical devices are reimbursed which are clinically and economically effective. HTA is a comprehensive process to evaluate the social, economic, organisational and ethical issues of a health technology. It becomes increasingly important for reimbursement decisions.
Based on HTA assessment national or local health care policy determines which medical devices will qualify for reimbursement by the government or healthcare insurances.
In some of the EU Member States, product pricing is determined by negotiation between the individual hospital and the medical device company. In most Member States a system of Diagnosis Related Groups (DRG) is used to set a price for a particular medical procedure, including any medical device that will be used in this procedure.

International, European and National Standardisation Environment

An important aspect especially for medical devices is to be compliant with international and European standards. There are general standards such as for quality management, terminology and nomenclature, metrology and instrumentation, or health safety and environmental practices. Standards becoming more relevant for the new smart medical devices are those for electrotechnical engineering or telecommunication. New products have to match the standards in these frameworks or they can set a new standard.
The following organisations are the most relevant ones at EU and international level.

International

The International Organisation for Standardisation (ISO)[25], the International Electrotechnical Commission (IEC)[26] and International Telecommunication Union (ITU)[27] are the relevant standardisation bodies at an international level.

[23] https://ec.europa.eu/growth/tools-databases/nando/index.cfm?fuseaction=country.main
[24] https://eunethta.eu/about-eunethta/eunethtanetwork/
[25] https://www.iso.org/home.html
[26] https://www.iec.ch/
[27] https://www.itu.int/en/Pages/default.aspx

Europe

Corresponding standardisation bodies at European level are the European Committee for Standardisation (CEN)[28], the European Committee for Electrotechnical Standardisation (CENELEC)[29] and the European Telecommunications Standards Institute (ETSI)[30], all three are officially recognised as European Standardisation Organisations.

National

The relevant National Standards Bodies (NSBs), e. g. DIN (German Institute for Standardisation) or DKE (German Commission for Electrical, Electronic & Information Technologies of DIN and VDE) represent national interests as members in the ISO, IEC, CEN and CENELEC organisation.

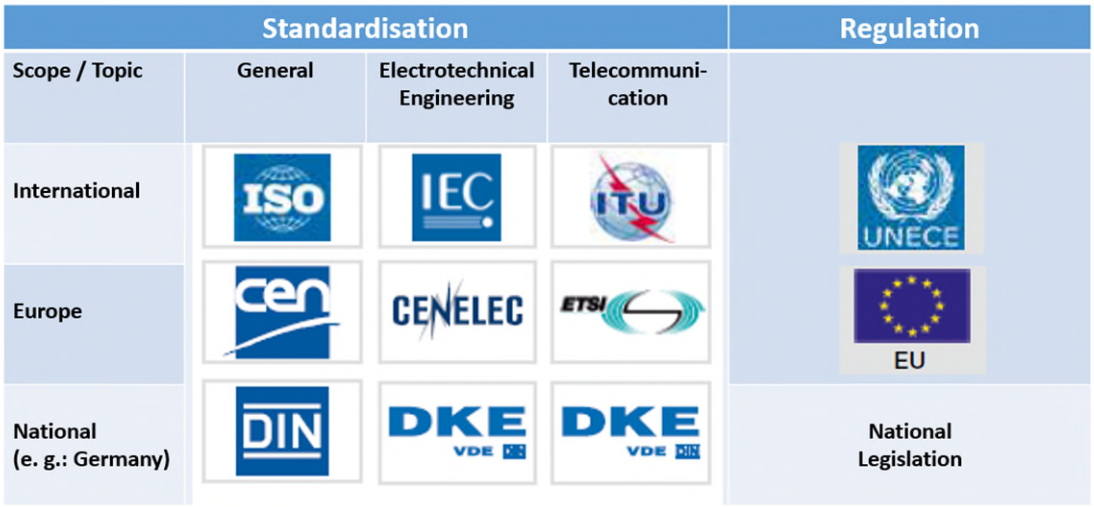


Figure 6: International Standardisation Environment[31]

Legislation

The Regulation (EU) No 1025/2012 of the European Parliament and of the Council of 25 October 2012 on European standardisation[32] establishes rules regarding the cooperation between European Standardisation Organisations, National Standardisation Bodies, Member States and the Commission.

Europe

CEN - Founded in 1961 and located in Brussels, the European Committee for Standardisation (**CEN**), an international non-profit association, comprises the National Standardisation Bodies of 34 European countries as a platform for the development of European Standards. These include various types of products, services and processes. It is responsible for European standardisation in all technical fields besides electro-technical engineering and telecommunication. As a practical example, the technical committee CEN/TC 251 Health informatics works on the topic of interoperability of health information systems in Europe.
The Members of CEN[33] are the National Standardisation Bodies of 34 European countries (these include all Member States of the European Union).

[28] https://www.cen.eu/Pages/default.aspx
[29] https://www.cenelec.eu/
[30] https://www.etsi.org/
[31] Source: DKE/VDE „Sichere dynamische Vernetzung in Operationssaal und Klinik": https://e-health-com.de/fileadmin/user_upload/dateien/Downloads/VDE_DKE_Weissbuch_Vernetzung_im_Operationssaal_2014.pdf, p20
[32] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=celex%3A32012R1025
[33] https://standards.cen.eu/dyn/www/f?p=CENWEB:5

CENELEC - The European Committee for Electrotechnical Standardisation (**CENELEC**), an international non-profit association, was founded in 1972 as a merger of two preceding European organisations, CENELCOM and CENEL, and is located in Brussels. It is the responsible authority for European standardisation in electro-technical engineering, thus promoting international trade, approach to new markets and reducing costs. CEN and CENELEC cooperate on joint activities, among others, in the domains of ecodesign, smart technologies, eMobility etc. and run a common website[34].
The National Electrotechnical Committees of 34 European countries are the members of CENELEC[35]. European Standards (ENs) and other standardisation deliverables taken over by CENELEC are accepted in all of these countries.
For strategic issues concerning CEN and CENELEC, the CEN-CENELEC Presidential Committee (Presidents and Vice-Presidents of CEN and CENELEC) is authorised by both organisations to address these issues accordingly. Relevant topics are: International cooperation activities, relations with European institutions, the set-up of joint advisory bodies or working groups (CEN-CENELEC SME Working Group etc.).

ETSI - The European Telecommunications Standards Institute (**ETSI**), a non-profit association founded in 1988 and located in Sophia Antipolis, France, produces standards for Information and Communications Technology (ICT), e. g. fixed, mobile, radio, broadcast and internet technologies. It addresses the lack of ICT standards, notably for the interoperability related to the eHealth area, and offers services for interoperability checks. Published ETSI standards mainly cover three main areas: Multimedia services for companies and private households; end devices for private mobile communication; and universally applicable (geographically and information transfer of all kinds) next generation networks. The size of its 800 global members[36] ranges from regulatory bodies over large-scale enterprises in the ICT branch to small companies. In contrast to the idea of National Regulation Bodies being the members of ISO/IEC/CEN/CENELEC organisations, ETSI is an open platform which allows its members, regardless of their size and background, to directly participate in the process of standards development.

The European Commission has identified five priority domains: 5G, cloud, cybersecurity, big data and the internet of things (IoT). In these domains, it considers ICT standardisation most urgent for the completion of the digital single market. Based on a broad stakeholder input, the **2019 Rolling Plan for ICT Standardisation**[37] provides a detailed picture on ongoing standardisation activities as well as standardisation and market needs in general.

International

ISO - The International Standardization Organisation (**ISO**), an association according to Swiss law and founded in 1947, is a global network of National Standards Bodies (no companies and no individuals are admitted). It is active in all domains except for the electro-technical and the telecommunication field. One member each per country represents ISO in its own country. The CEN members (34) form part of the 164 ISO members[38].
ISO differentiates between three categories of membership:

1. Full members influence ISO standards, participate in the meetings and sell/adopt ISO International Standards nationally;
2. Correspondent members – observe the development of ISO standards, participate in the meetings as observers and sell/adopt ISO International Standards nationally; and
3. Subscriber members – keep up to date on ISO's work, cannot participate in it or sell/adopt ISO International Standards nationally.

To view the development process of a new ISO international standard, please click here[39].
Common ISO standards are:

- ISO 9001:2015 – Quality Management Standard for companies and organisations
- ISO Standard Medical Devices ISO 13485:2016
- ISO 31000:2018 - Risk Management – Guidelines and processes for organisation regardless of size for managing risks
- ISO 45001 - Occupational Health and Safety reducing workplace risks

[34] https://www.cencenelec.eu/aboutus/Pages/default.aspx
[35] https://www.cencenelec.eu/News/Publications/Publications/CEN-CENELEC%20Annual%20Report%202018.pdf, p 170
[36] https://www.etsi.org/index.php?option=com_content&view=article&id=23:current-members&catid=16:membership&Itemid=124
[37] https://ec.europa.eu/docsroom/documents/34788
[38] https://www.iso.org/members.html
[39] https://www.iso.org/developing-standards.html

IEC

The International Electrotechnical Commission (IEC), founded in 1906 and located in Geneva, Switzerland, is the world's leading (non-profit) organisation for the preparation and publication of International Standards for electrotechnology (electrical, electronical and related technology). It also conducts Conformity Assessment for these techniques, comprising all devices which contain electronics and use or produce electricity.

The IEC members[40] (currently: 87) are individual National Committees (NCs). Only one per country is allowed. Being involved in the development of a standard, a NC ascertains that the interests of its country have been considered accordingly. Two levels of Membership are permitted:

- **Full members** – The NC has access to all technical and managerial activities and functions of the IEC, including voting rights.
- **Associate members** - NC has full access to all working documents but limited voting rights.

The IEC provides a network within participants can communicate with customers, manufacturers, technical experts and government representatives and an environment where small companies and countries meet as equal partners with big companies and big countries.

ITU

The International Telecommunication Union (ITU), located in Geneva, Switzerland, has originally been founded on 17th May 1865 as International Telegraph Union. 193 Member States[41] and about 900 companies, universities and organisations have joined the ITU, which is a special agency of the United Nations. The ITU internationally coordinates the use of the radio spectrum; promotes cooperation in assigning satellite orbits; works to improve telecommunication infrastructure in the developing world and assists in the development and coordination of worldwide technical standards. Moreover, it is active in the areas of broadband Internet, latest-generation wireless technologies, satellite-based meteorology, Internet access, data, voice, TV broadcasting, next-generation networks and others.

World Standards Cooperation (WSC)

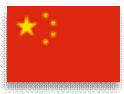
This is the alliance of the above-mentioned, international standardisation organisations ISO, IEC and ITU.

[40] https://www.iec.ch/dyn/www/f?p=103:5:0##ref=menu
[41] https://www.itu.int/en/ITU-R/terrestrial/fmd/Pages/administrations_members.aspx

International Regulatory Processes

Beyond the existing (complex) system for regulation in Europe, providers of healthcare products may address further international markets and therefore need to dispose of basic information on regulatory issues in significant markets. NOBEL provides in the following pages a series of quick overviews, links to relevant documents and contacts for a selection of countries of major interest:


USA


China

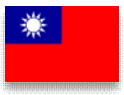

Japan


India


Brazil


South Korea


Canada


Taiwan

Regulatory Processes in the USA

Regulatory Environment

In contrast to the European regulatory systems with many different agencies and approval processes, only the **Food and Drug Administration (FDA or USFDA)**[42] is responsible in the US for the evaluation and approval of both medicinal products and medical devices. FDA is a Federal Agency of the United States Department of Health and Human Services, responsible for protecting and promoting public health through the regulation and supervision of areas ranging from food safety, vaccines, medicinal products, medical devices, cosmetics and veterinary products.

FDA represents the entry portal for approval of all drug and medical devices. The main criteria for approval are safety, efficacy, and quality. Along these three pillars all products including nano-based products are evaluated.

FDA is organised in several centres dedicated to a specific area. In March 2019, FDA started a reorganisation[43] of the agency in order to modernise its structure and to meet the challenges of rapid innovation across the industries regulated by FDA. The Center for Drug Evaluation and Research (CDER)[44] is dealing with the approval of drugs while the Center for Devices and Radiological Health (CDRH)[45] is handling medical devices and IVD products.

Legal Framework

The Federal Food, Drug and Cosmetic Act (FD&C Act)[46] is a set of laws giving authority to the FDA to oversee the safety of food, drugs, medical devices, and cosmetics. Moreover, FDA published several Guidance Papers[47] related to Nanotechnology Applications, for example, which specifically deal with nanomedicine. For a further overview, please check as well the following relevant information[48] and guidance documents[49] for drugs.

Approval Process for Drugs

On completion of the preclinical testing phase, the sponsor files an Investigational New Drug Application[50] (IND) to the FDA seeking permission to start clinical trials in humans. It includes initial test results, information on the drug's composition and manufacturing and a plan for testing the drugs on humans. On approval by FDA and by an Institutional Review Board, the

[42] https://www.fda.gov/
[43] https://www.fda.gov/about-fda/fda-organization
[44] https://www.fda.gov/about-fda/fda-organization/center-drug-evaluation-and-research-cder
[45] https://www.fda.gov/about-fda/fda-organization/center-devices-and-radiological-health
[46] https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act
[47] https://www.fda.gov/science-research/nanotechnology-programs-fda/nanotechnology-guidance-documents
[48] https://www.fda.gov/drugs/types-applications/new-drug-application-nda
[49] https://www.fda.gov/drugs/guidances-drugs/newly-added-guidance-documents
[50] https://www.fda.gov/drugs/types-applications/investigational-new-drug-ind-application

manufacturer may start the first phase of Clinical Trials. The requirements for content and format of an IND are specified in 21 CFR Part 312[51].

During Phase I, II and III of these trials, safety, dosing, efficacy and side effects are being tested. As soon as Phase III is completed, FDA and the sponsor have a review meeting. As next step, the drug sponsor submits a New Drug Application[52] (NDA) to the FDA which is the formal request for FDA's approval to manufacture and to sell the drug in the USA. The NDA includes all animal and human test data, their analyses and the information how the drug is manufactured and its behaviour in the body. The content and format of an NDA is laid out in 21 CFR Part 314[53] (Code of Federal Regulations).
On receipt of an NDA, FDA decides within 60 days whether to file it for review. At this stage, the drug undergoes a detailed evaluation and review. In order to obtain sufficient data on drug safety, effectiveness, adverse events and other criteria, FDA consults advisory committees prior to granting approval. Moreover, the drug's professional labelling and adequate information for consumers are being reviewed. An FDA inspection of the drug manufacturing plant follows to ensure that the drug is produced according to FDA's Current Good Manufacturing Practices[54] (CGMP).
In order to obtain approval of Generic Drugs, a sponsor is not requested to repeat clinical studies which have been conducted for the original product. He may submit an Abbreviated New Drug Application[55] (ANDA). The sponsor has to provide data and information which prove that the drug is pharmaceutically equivalent to the predicate product and that the proposed use and labelling is identical to the reference (innovator) drug.
In case of an urgent medical need or breakthrough therapy, FDA offers an accelerated approval process (Fast Track)[56] in order to expedite review and approval of drugs.
One should be aware of the fact that a product classified as a drug in Europe can be regarded as a medical device by FDA or vice versa. Example is NBTXR3[57], lead NanoXray product of company Nanobiotix which is classified as a drug in the USA by the FDA, while this product is regarded as a medical device in Europe.
When a drug has been approved, the post-marketing monitoring stage starts, e.g. the manufacturer has to periodically submit safety updates to FDA. This shall enable FDA to detect serious adverse events in due time and to take counteractive measures.

Approval Process for Medical Devices

A manufacturer without a facility in the USA has to appoint a US Agent representative as a direct contact to the FDA. Amongst other tasks, the agent assists in the communication with the FDA and schedules FDA inspections of the facilities. Owners of an establishment producing and distributing medical devices for use in the United States must register annually with the FDA.
As a first step of the regulatory pathway, the MD or in vitro diagnostic device (IVD) has to be classified either by consulting the FDA classification database[58] or the FDA device classification panel[59] which indicates medical specialties.
The Medical Device Amendments of 1976 to the Federal Food, Drug and Cosmetic Act[60] define three regulatory classes for medical devices with an ascending degree of control to assure safety and effectiveness of devices:

Class I (low to moderate risk) – These devices present minimal potential for harm to the user, e. g.: thermometers, elastic bandages. FDA has exempted[61] almost all class I devices from the premarket notification requirement (with the exception of Reserved Devices[62] – these remain subject to premarket notification). The exempted Class I devices are subject to general control requirements such as records and reports provided by the manufacturer.

[51] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRsearch.cfm?CFRPart=312
[52] https://www.fda.gov/drugs/types-applications/new-drug-application-nda
[53] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=314
[54] https://www.fda.gov/drugs/pharmaceutical-quality-resources/current-good-manufacturing-practice-cgmp-regulations
[55] https://www.fda.gov/drugs/types-applications/abbreviated-new-drug-application-anda
[56] https://www.fda.gov/patients/learn-about-drug-and-device-approvals/fast-track-breakthrough-therapy-accelerated-approval-priority-review
[57] https://www.nanobiotix.com/healthcare-professionals/
[58] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/classification.cfm
[59] https://www.fda.gov/medical-devices/classify-your-medical-device/device-classification-panels
[60] https://www.fda.gov/regulatory-information/laws-enforced-fda/federal-food-drug-and-cosmetic-act-fdc-act
[61] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm
[62] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/3151.cfm

Class II (moderate to high risk) devices require the 510(k) Premarket Notification[63] (PMA), e.g.: Diagnostic tests, cardiac catheters, hearing aids. FDA has published a list of class II (special controls) devices subject to certain limitations, that are exempt[64] from premarket notification requirements.

In addition to the (Traditional) route of the 510(k) Premarket Notification, two further routes exist: The Special 510(k) PMN as an accelerated procedure for modifications of the own device and the Abbreviated 510(k) PMN which allows the submission of a reduced documentation if the manufacturer adheres to recognised standards, FDA guidance documents and special controls.
Class III (high risk) – These devices usually sustain or support life, e.g. implantable pacemakers, breast implants and automated external defibrillators. These high-risk devices are approved by the Premarket Approval[65] (PMA) process.
For Class III devices, a premarket approval application (PMA) will be required unless your device is a pre-amendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device). In that case, a 510k will be the pathway to market.
A Quality Management System (QMS) has to be implemented for classes II and III.
If clinical trials are required (classes II and III), the sponsor has to apply for an Investigational Device Exemption[66] ensuring that the investigational device may be used in order to collect safety and effectiveness data. A clinical trial protocol has to be set up und the studies have to be conducted. Moreover, facility inspections of all major suppliers of class III devices will be executed.
In case of approval, FDA issues a 510(k) clearance letter for Class II MDs and a PMA approval letter for Class III MDs and publishes them online. Company authorisation for marketing the device in the USA remains valid as long as no changes are made to the intended use, design etc. For additional information, please follow the links regarding FDA medical device approvals[67] and on the different submission methods[68].
For new devices classified as Class III by default (low or moderate risk), a manufacturer may ask for a classification as "de novo" device[69] in order to avoid the more complex Premarket Approval process. He either chooses the 510(k) PMN application and - in case of rejection from the FDA - submits a de novo application as second step. Alternatively, he directly applies for the de novo route (direct de novo), assessing his product as a new device (Class I or II).
For medical devices which treat or diagnose a disease affecting not more than 200,000 individuals per year, the Humanitarian Device Exemption[70] (HDE) is a FDA review process for these medical devices (Class III) and exempt from the effectiveness requirements of Sections 514 + 515 of the FD&C Act.

Regulatory Processes in China

Regulatory Environment

The **National Medical Products Administration (NMPA)**[71], replaced former China Food and Drug Administration (CFDA) in 2018. It is responsible, amongst other functions, for the supervision of safety of drugs and medical devices; the regulation of drug and medical devices registration; the conducting of review and approval for marketing. Moreover, it undertakes quality management for drugs and medical devices, develops and supervises the implementation of Good Laboratory Practices (GLP), Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP). It is therefore the entry portal for the approval of drugs and medical devices and reports to the Ministry of Health (MOH). Approval procedures are performed by the Department of Drug Registration (five divisions including the Division of Traditional Chinese Medicines and Ethno-Medicines and the Division of Biological Products) and by the Department of Medical Device Registration.

[63] https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpcd/315.cfm
[64] https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma
[65] https://www.fda.gov/medical-devices/premarket-submissions/premarket-approval-pma
[66] https://www.fda.gov/medical-devices/how-study-and-market-your-device/investigational-device-exemption-ide
[67] https://www.fda.gov/medical-devices/products-and-medical-procedures/device-approvals-denials-and-clearances
[68] https://www.fda.gov/medical-devices/premarket-notification-510k/510k-submission-programs
[69] https://www.fda.gov/medical-devices/premarket-submissions/de-novo-classification-request
[70] https://www.fda.gov/medical-devices/premarket-submissions/humanitarian-device-exemption
[71] http://english.nmpa.gov.cn/

Regulatory Framework

Important Laws and Regulations to be known are: The Pharmaceutical Administration Law of the People's Republic of China[72]; Regulations for Implementation of the Drug Administration Law of the People's Republic of China[73]; Provisions for Drug Registration[74] (2007, updated 25.07.19), Special Review and Approval Procedure for Drug Registration of the China Food and Drug Administration.

Approval Process for Drugs

In order to obtain marketing authorisation, new drugs must successfully pass pre-clinical research according to Good Laboratory Practices (GLP); approval for clinical trials from **Center for Drug Evaluation** (CDE); clinical trials according to Good-Clinical-Practice (GCP; phase I – III) and the new drug application for production approval.

On 1st Dec., 2019, amendments to the Drug Administration Law (DAL) entered into force. They include a new regulatory framework, a drug traceability system and the establishment of a **Drug Marketing Authorisation Holder** (MAH). The Drug Marketing Authorisation Holder (company or research institution that has obtained a drug registration certificate) is legally responsible for the safety, efficacy and quality control of drugs during the entire life span (development, production, distribution and use.
Foreign enterprises are allowed to hold a Chinese drug marketing authorisation. They have to nominate before, however, a Chinese company to meet the obligations, and the two enterprises have to perform several liabilities.

Approval Process for Medical Devices

First step in the regulation of medical devices (MD) is to define their risk classification (class I – III) according to the NMPA Medical Device Classification Catalogue and to check if the device is on the clinical trial exempt list.
An Agent who is based in China needs to be appointed for the coordination of the device registration. If the device has already been approved in and is available on the home country market, the manufacturer needs to present a documental proof, e. g. Certificate of Free Sale (CFS). Moreover, the manufacturer has to submit proof of ISO 13485 certificate or equivalent documentation and a dossier with foreign and local test reports. For Class I devices, foreign test documentation is generally accepted; class II and III devices additionally require local test reports.
For all Class II and III medical devices, **a Clinical Evaluation Report** (CER) stating the data and results of a clinical evaluation is required. It is either the:

a) (Simplified) CER for clinical exemption and published on the NMPA list of exempted devices
b) (Full) CER for clinical unexempt.

In some cases, additional specific technical information may be required for certain products. If a highly equivalent product has already been approved in China, a comparative study is needed in the manufacturer's report. NMPA finally decides if a CER is sufficient or not.
For Class I, a technical documentation has to be submitted to the NMPA (no fees); for Class II and III, a dossier which includes Agent authorisation letter, test reports, CFS and other technical documents. Whereas Class I devices will run through an administrative review only, Class II + III devices will pass a full (administrative and technical) application review including an optional on-site QMS audit, executed by the NMPA.
In case of approval, NMPA confirms the registration and publishes it on the website. Class I registration does not expire, Class II and III registration is valid for five years. At the end of this period, a comprehensive re-assessment is required. The device may now be marketed in China.
The assistance of an expert service provider in this process is recommended due to the fact that the documentation for NMPA's evaluation requires translation into Chinese language.
Manufacturers have to check if, in addition, a CCC certification (China Compulsory Certificate, a compulsory safety mark for many products) is required for their product. The **China Quality Certification Center (CQC)[75]** conducts CCC mark applications

[72] https://www.fmprc.gov.cn/ce/cgvienna/eng/dbtyw/jdwt/crimelaw/t209042.htm
[73] https://sherloc.unodc.org/res/cld/document/chn/regulations-for-implementation-of-the-drug-administration-law-of-the-peoples-republic-of-china_html/Regulations_for_Implementation_of_the_Drug_Administration_Law_of_the_Peoples_Republic_of_China_2002.pdf
[74] http://english.nmpa.gov.cn/2019-07/25/c_390615.htm

[75] https://www.cqc.com.cn/www/english

and determines if the products needs the CCC. Certification procedure involves additional specific product tests and factory audits.

Regulatory Processes in Japan

Regulatory Environment

The **Pharmaceuticals and Medical Devices Agency** (PMDA)[76] is an independent administrative legal authority. It provides, among other functions, the advice for clinical trials; the scientific review of market authorisation applications including the evaluation of quality, efficacy and safety of drugs, medical devices, cellular and tissue-based products; the inspection and assessment of Good Clinical Practice (GCP), Good Laboratory Practice (GLP) and Good Practice Systems and Programs (GPSP) as well as the auditing of manufacturers. It is the entry portal for the approval of drugs and medical devices, headed by the **Ministry of Health, Labour and Welfare** (MHLW)[77]. According to the PMDA's review results, the MHLW formally approves or rejects the relevant drug or MD.
Various laws and regulations provide the basis for pharmaceutical administration in Japan, among them are the Pharmaceutical Affairs Law (PAL), the Law Concerning the Establishment for Pharmaceuticals and Medical Devices Organization, and the Law Concerning Securing Stable Supply of Blood Products.

Legal Framework

On 25th Nov. 2014, the **Pharmaceutical and Medical Device Act (PMD Act)** has been launched. It is entitled „Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products and Cosmetics" and revises the former Pharmaceutical Affairs Law (PAL). In addition to the PAL, the PMD Act includes regenerative and cellular therapy products and gene therapy products.
Foreign companies that wish to produce and import drugs or medical devices abroad and import them to Japan have to apply for a **Foreign Manufacturers Registration**[78] (FMR) of the company with the MHLW. This process is independent of the product approval process and necessary for obtaining product registration approval. It includes an audit by the PMDA, in some cases an additional on-site inspection.

Approval Process for Drugs

Only a Marketing Authorization Holder (MAH) - which can be a distributor with a MAH license, a regulatory consulting firm or a licensed manufacturer - can submit an approval application to the PMDA. Foreign companies without a branch in Japan may authorise a Japanese MAH accordingly.
On receipt of the application form, review teams of the PMDA undertake a compliance review of the data, a GCP on-site inspection and a detailed review. The teams prepare a report; and important problems will be discussed with external experts. On completion of the review report, it will be sent to the Ministry of Health, Labour and Welfare. The Pharmaceutical Affairs and Food Sanitation Council (PAFSC) will be consulted for additional advice. The MHLW finally grants the new drug manufacturing approval.

[76] https://www.pmda.go.jp/english/about-pmda/index.html
[77] http://www.mhlw.go.jp/english/
[78] https://www.pmda.go.jp/english/review-services/reviews/foreign-mfr/0001.html

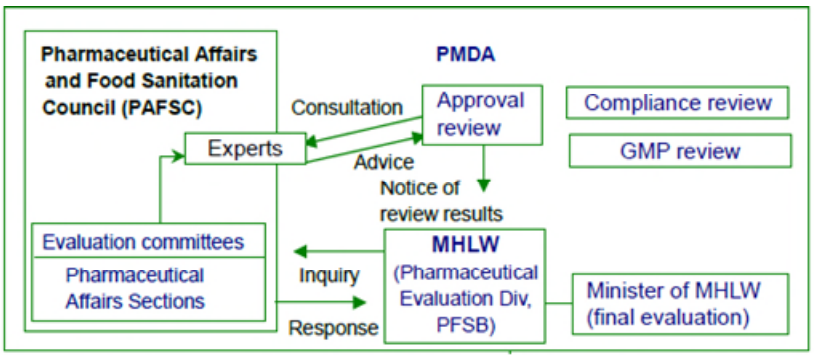


Figure 7: Flowchart of Drug Approval Review[79]

Approval Process for Medical Devices

First step of the regulatory pathway of an MD in Japan is the selection of a **Marketing Authorization Holder (MAH)** i.e. the company which manages the device approval process and is responsible for all aspects of the product, including quality and compliance with the conditions of the marketing authorisation.

Then the MD has to be classified. Four classes exist:

1. General MDs (Class I) with a low risk such as X-Ray films or scalpels. For this regulatory process called „Notification", a Pre-Market Submission with a detailed device description (materials used, measurements etc.) to the PMDA is requested. A QMS audit is not necessary.
2. Specified Controlled MDs (Class II) with a low/medium risk, e. g. MRI Magnetic Resonance Imaging equipment, need a third party review of a Registered Certified Body (RCB). For this regulatory process called „Certification", a Pre-Market Certification application has to be sent to a RCB. A QMS audit will be conducted by the Registered Certification Body (RCB). Documents for Controlled MDs (Class II) with medium risk have to be submitted to the PMDA and undergo a QMS audit by PMDA, as well as all MDs of Classes III + IV:
3. Highly controlled MDs (Class III) with medium/high risk, e. g. Dialyzers, Artificial bones and
4. Highly controlled MDs (Class IV) with high risk, e. g. pacemaker, artificial heart valves which require PDMA's review and Minister's approval.

All documents have to be submitted in Japanese language.
A Quality Management System (QMS) has to be implemented, for all classes, in accordance with the **PMD Act and MHLW Ordinance #169**[80], which is comparable to ISO 13485. In case of a positive review, a QMS certificate will be issued by RCB or PMDA with a validity of five years. In case of medical device approval, the manufacturer may start marketing the device in Japan. A device registration does not expire.

Regulatory Processes in India

Regulatory Environment

The **Central Drugs Standard Control Organisation (CDSCO)**[81] is the national regulatory body and entry portal for regulation and approval of pharmaceuticals and medical devices in India. It operates under Directorate General of Health Services (DGHS) which is part of the **Ministry of Health and Family Welfare**[82]and holds six zonal offices, four sub zonal offices, thirteen port offices and seven laboratories across the country. Among other functions, CDSCO is responsible for conducting clinical trials, establishing drug standards, monitoring the quality of drug imports and supervising the Drugs Consultative Committee and Drugs Technical Advisory Board meetings.

[79] http://www.jpma.or.jp/english/parj/pdf/2019.pdf, p 91
[80] https://www.safetyweb.co.jp/files/medical_equipment/mhlw_no169_20140730.pdf
[81] https://cdsco.gov.in/opencms/opencms/en/Home/
[82] http://mohfw.gov.in/

Within the CDSCO, the **Drug Controller General of India (DCGI)** is the main licensing authority which directly issues permission for new drugs and specific medical devices and for the manufacturing of certain drugs.

In January 2016, CDSCO introduced the online portal SUGAM for the submission of applications relating to drugs, clinical trials, medical devices, vaccines permission and requests for the ethics committee. It serves as well as a database of approved drugs, manufacturers, formulations and others in India.

Legal Framework

The Drugs & Cosmetic Act 1940 and Rules 1945[83] regulates the manufacturing, import, sale and distribution of Drugs and Medical Devices as well as clinical trials.

Approval Process for Drugs

The drug manufacturer has to submit his request under the provisions of this Act in order to obtain permission to import or manufacture a new drug or to undertake clinical trials. A Common Technical Document - covering administrative and legal information, a product summary, quality, nonclinical and clinical issues - has to be presented as well. In addition, the manufacturing site has to be registered for import activities.
According to Rule 122-A of the Drugs and Cosmetics Act, already existing international clinical trial data or other information can replace an additional clinical trials procedure in India. The same applies to drugs that have been approved and marketed in other countries for a long time.
A **drug approval process**[84] is described on the CDSCO website.

Legal Framework for Drugs / Medical Devices

Additional important regulations and provisions are:

- Guidance document on application for grant of Licence in Form-28 for manufacture of Medical Devices in India under CLAA-Scheme[85];
- Guidance document on Common Submission Format for Import License in Form-10 of Notified Medical Devices in India[86];
- Guidance document on Common Submission Format for Registration/Re-Registration of Notified Medical Devices in India[87];
- Guidance for Industry on Submission of Clinical Trial Application for Evaluating Safety and Efficacy/Requirements for permission for New Drugs Approval[88].

As a result of reprocessing medical devices regulatory procedures, the **Medical Device Rules 2017**[89]came into effect on January 1, 2018. The new rules provide a regulation of medical devices based on international standards and on the principals of the Global Harmonisation Task Force (GHTF). In the meantime, the GHTF has been replaced by the International Medical Device Regulators Forum[90] (IMDRF).

Integral parts of the new Medical Device Rules:

- Classification of MDs into **four classes** (Class A - D);
- **Quality Management System** (QMS) for all manufacturing sites will be aligned with ISO 13485;
- A structure of **Notified Bodies**, accredited by the National Accreditation Board for Certification Bodies (NABCB), will be implemented;

[83] https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016DrugsandCosmeticsAct1940Rules1945.pdf
[84] https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/New-Drugs/Process/NDD_APPL_Organogram.pdf
[85] http://www.msk.nclinnovations.org/medregulations/v1/html/Guidance/Guidance_Form%2028%20Manufacturing%20License.pdf
[86] https://elsmar.com/elsmarqualityforum/attachments/import-license-in-form-10-of-notified-medical-devices-in-india-pdf.16374/
[87] https://elsmar.com/elsmarqualityforum/attachments/registration_-re-registration-of-notified-medical-devices-in-india-pdf.16375/
[88] https://www.kem.edu/wp-content/uploads/2019/12/CDSCO-Guidance-For-Industry.pdf
[89] https://morulaa.com/cdsco/medical-devices-rules-2017-classification-of-medical-devices/
[90] http://www.imdrf.org/about/about.asp

- **Manufacturing** and import licences will remain valid until they are cancelled with no periodic renewal of licences in future.

Approval Process for Medical Devices

As first step in the regulatory pathway, the MD has to be classified. Four classes with an ascending risk exist as follows: Class A - Low Risk, Class B - Low-moderate Risk, Class C - Moderate-high risk, Class D - High Risk. For the **CDSCO's list of Classification of medical devices and IVDs**, click here[91].
Companies, which want to market medical devices in India but are without a registered office, have to appoint an India Authorised Agent holding a valid wholesale license.

CDSCO has a:

- **State Licensing Authority** (SLA) with responsibility for Class A and B devices Medical Devices Manufacturing, Loan and Wholesale Licenses. SLA determines a Notified Body to confirm the requirements of Quality Management System and Technical Review for Class A & Class B Medical Device Manufacturers.
- **Central Licensing Authority** (CLA) with responsibility for all Import Devices Licensing and Class C & Class D Medical Devices Manufacturing, Loan and Wholesale Licenses. CLA may utilise the services of a Notified Body for inspecting the manufacturing site of Class C and Class D medical devices and Technical Review.

The DCGI reviews the application, sends back an inquiry letter and may additionally ask for a technical presentation (personal meeting of a representative from the manufacturer, together with the India Authorised Agent, with CDSCO for in-depth discussion about the product). Clinical data may not be necessarily requested if foreign clinical data are available and acceptable.
In case of a positive documentation review, MD approval (license) is granted.

Regulatory Processes in Brazil

Regulatory Environment

The **Agência Nacional de Vigilância Sanitária or Brazilian Health Regulatory Agency** (ANVISA)[92], created in 1999, is an independently administered and financially autonomous regulatory body of the Brazilian government. The agency which is the entry portal for the regulation and approval of drugs and medical devices is managed by a Collegiate Board Of Directors and linked to the Ministry of Health. Among other functions, it is responsible for establishing of regulations for clinical trials and drug prices, the monitoring of drug and MD prices and the inspection of factories in order to supervise the quality of drugs. Moreover, it analyses patent requests regarding pharmaceutical products and processes, in cooperation with the **Brazilian Patent Office**, Instituto Nacional da Propriedade Industrial (INPI)[93].

Foreign companies cannot make arrangements for issuing market authorisations directly with Anvisa. These companies need a partner company legally constituted in Brazil that will be legally responsible for the products imported to and distributed in Brazil.

Legal Framework

Important Federal Laws, Resolutions to be known are:

- Law 5991/73, regulated by Decree 54170/74 setting the sanitary control of the drug trade, drugs and active pharmaceutical ingredients;

[91] https://cdsco.gov.in/opencms/opencms/system/modules/CDSCO.WEB/elements/download_file_division.jsp?num_id=NDM5Ng==
[92] http://portal.anvisa.gov.br/contact-us
[93] http://www.inpi.gov.br/english

- Law 6360/76, regulated by Decree 74170/77, controlling the production of medicines;
- Resolution 136/2003 for the registration of new medicines;
- Act 6360/1976 – Legal provision for product registration;
- Act 6437/1977 – Violations of federal health legislation and their respective sanctions;
- Act 8080/1990 – Consumer rights and general provisions;
- Decree 8077/2013 – Health Surveillance.

In 2016, ANVISA became a member of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)[94].

Approval Process for Drugs

Documents, which have to be submitted for the registration procedure of a new drug are:

- protocols of the clinical studies as well as registration petition forms,
- a proof of payment of Sanitary Surveillance Inspection,
- a copy of the Company's Operation License, and
- a Technical Responsibility Certificate.

Moreover, a Good Manufacturing Practices certificate (GMP) is required of each importer of a product into Brazil.

Approval Process for Medical Devices

A foreign medical device manufacturer without a site in Brazil has to appoint a **Brazilian Registration Holder** (BRH) who acts as a regulatory representative.
Brazil's medical device classification schemes are similar to those outlined in the European MDD 93/42/EEC. The MD has to be classified according to ANVISA Resolution RDC 185/2001; 40/2015; 36/2015.
Four classes with an increasing risk exist: Class I (low), Class II (medium), Class III (high) – Class IV (maximum).

- The **Cadastro** registration applies for Class I + II, which is a simplified pathway requesting a reduced technical dossier and the Brazil Good Manufacturing Practice certification (BGMP), but no audit. The approval certificate does not need to be renewed.
- Class III + IV follow the **Registro** pathway, which is more time-consuming and additionally stipulates an audit according to ANVISA resolution RDC 16/2013. A GMP certification and a technical dossier including clinical data, clinical studies and additional device information has to be presented. Approval is valid for 10 years and has to be renewed.

In general, devices registered through the Cadastro pathway can be licensed within 4-6 months and, through the Registro pathway, within 8-10 months.
Most electrical MDs and some non-electrical MDs additionally need a certification by **The National Institute of Metrology, Standardisation and Industrial Quality** (INMETRO)[95]. INMETRO is Brazil's standardisation body and responsible for the accreditation of each product Certification Body. The MD has to be tested and certified by a recognised Certification Body, who apply their own mark as well as the INMETRO seal of approval. INMETRO usually accepts electrical safety certifications which already exist if they had been carried out by International Laboratory Accreditation Cooperation certified laboratories (ILAC). On successful receipt of the INMETRO certification, the Brazil Registration Holder can prepare and submit the MD's application to ANVISA for further review and approval.
Brazil participates in the Medical Device Single Audit Program (MDSAP). MDSAP has been created to provide a single audit (mutual recognition of GMP certificates) for medical device manufacturers that is accepted in different regulatory legal frameworks.

[94] https://www.ich.org/
[95] http://www4.inmetro.gov.br/

Regulatory Processes in South Korea

Regulatory Environment

The **Ministry of Food and Drug Safety (MFDS)**[96]**,** previously known as Korea Food and Drug Administration, is the South Korean regulatory authority and the entry portal for the approval of drugs and medical devices. It is responsible for the establishment and revision of drug laws, the GMP inspection and evaluation of drugs and post-marketing safety control. It establishes and revises standards of medical devices, provides technical support for GMP management and re-evaluates safety and efficacy of MDs. It is linked to the **Ministry of Health and Welfare (MoHW)**[97] which takes the final decision of covering, coding and pricing of medical devices.

Legal Framework

Important laws to be known are:

- the Pharmaceutical Affairs Act[98] and
- the Medical Device Act.[99]

The National Law Information Center[100] as the Korean representative legal information web site is helpful for the research and identification of additional relevant law titles.

Approval Process for New Drugs

According to the Pharmaceutical Affairs Act, pharmaceuticals are classified into

a) drug products (new drugs, pharmaceuticals that require data submission, generic drugs) and
b) pharmaceutical ingredients.

New drugs have a chemical structure or original composition, which is clearly different from any product previously approved in Korea or are a product containing a new material as an active drug substance. Applications for the registration of a new drug require a lot of data concerning safety, efficacy, specifications and test methods, Drug Master Files and Good Manufacturing Practice.

A new drug application (NDA) is sent to the MFDS, and the application dossier for drug approval is presented to the MFDS Management Division for Dug Approval & Review. MFDS conducts an initial assessment of the application, prepares a report and sends it to the MFDS Drug & Evaluation Department. The MFDS Drug & Evaluation Department conducts a review including the results of the initial assessment, technology, safety & efficacy data, product standards, clinical trial data, GMP data, Drug Master File data etc. If no additional information is needed, the MFDS issues the Certificate of approval.
Pharmaceuticals which are not new drugs but requiring data submission have to provide safety and efficacy data for evaluation prior to be approved.

[96] https://www.mfds.go.kr/eng/index.do
[97] www.mohw.go.kr/eng/
[98] http://www.law.go.kr/eng/engLsSc.do?menuId=2&section=lawNm&query=Pharmaceutical+Affairs+ACT&x=26&y=23
[99] http://www.law.go.kr/eng/engLsSc.do?menuId=2&query=MEDICAL%20DEVICES%20ACT#liBgcolor6
[100] http://www.law.go.kr/eng/engMain.do

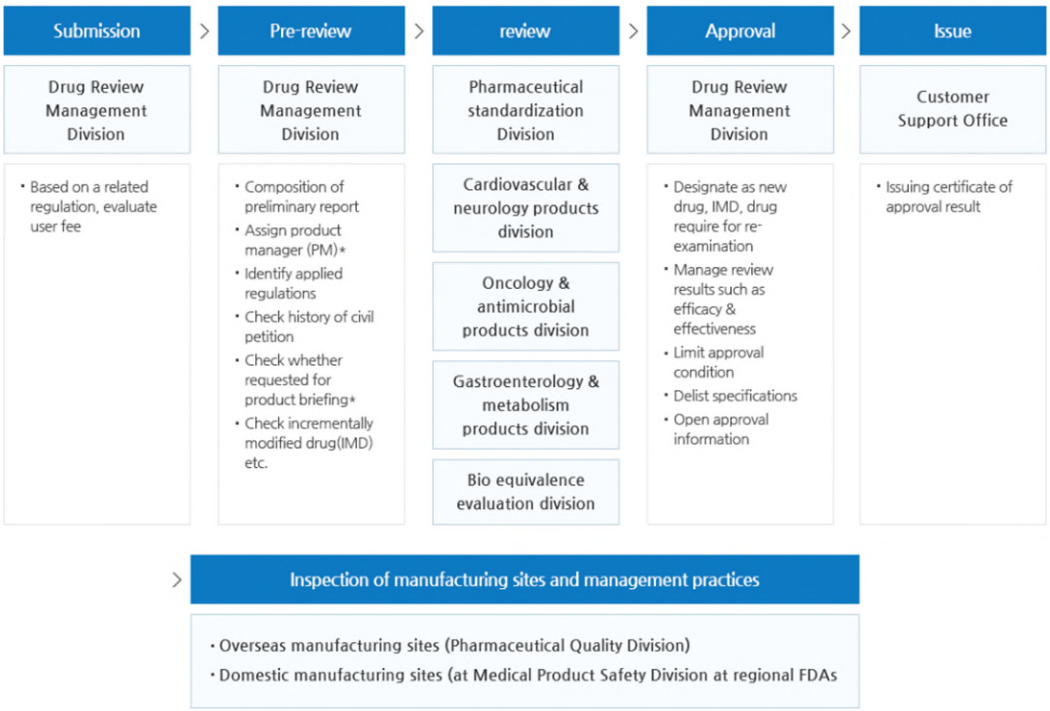


Figure 8: New Drug Marketing Approval[101]

Approval Process for Medical Devices

Manufacturers and distributors without a registered office who intend to market their MD in South Korea have to appoint a Korea License Holder (KLH). This is a legal representative, who is located in the country and coordinates the MD registration application to the MFDS. If a subsidiary exists, the subsidiary will be the license holder, and a consultant conducts the registration.
As next step, the MD has to be classified. Four classes (I – IV) according to an increasing risk for human health exist:

- Class I: little risk (e. g.: scissors, mechanical stethoscope) for which a pre-market notification is sufficient. It contains basic information and is sent to the National Institute of Medical Device Safety (NIDS), renamed and previously known as MDITAC (Information & Technology Assistance Center), a MFDS unit dealing with low risk MDs. A pre-market notification for Class I does not expire.

Prior to the medical device registration by MFDS, Classes II – IV have to pass a Korea Good Manufacturing Practices (KGMP) audit and certification according to the requirements of ISO 13485.

- For Class II devices, low risk (e. g.: syringe, infusion pumps), an on-site audit is carried out by a Third Party Auditor. After a successful review, the NIDS (most class II devices) will grant the final Pre-Market Approval licence.
- Classes III devices, moderate risk (e. g.: spinal cage), and Class IV devices, high risk (e. g.: coronary stent, cardiac pacemaker), will be audited by a Third Party Auditor and the MFDS. The certificate will be valid for three years. For novel Class II and Class III-IV devices, the MFDS will issue the final Pre-Market Approval licence.

If the MD (Classes II-IV) has a substantial equivalent already sold in Korea, the submission of a General Technical File (GTF) is expected by the MFDS. For Class II, third parties approved by the MFDS can evaluate the technical documentation.
Manufacturers of Class II - IV MDs without substantial equivalence have to prepare a SER Technical File (Safety and Effectiveness review) submission. Clinical data have to be included in the SER submission. In general, proven clinical trial data from OECD member countries will be accepted.
On approval of the medical device by MFDS, the applicant is authorised to market his device. Validity periods for device registrations (classes II-IV) do not expire as long as the MD and its usage remain unmodified.

[101] https://www.mfds.go.kr/eng/wpge/m_17/de011008l001.do

Regulatory Processes in Canada

Regulatory Environment

The Health Products and Food Branch (HPFB)[102] of Health Canada, the country's federal authority in charge of national health care, is the entry portal for the regulation, evaluation and monitoring of the safety, efficacy and quality of drugs and medical devices in Canada.
Prescription drugs and medical devices for human use are regulated by the Therapeutic Products Directorate (TPD)[103], one of the seven operational directorates of the HPFB. The regulatory authority for biological drugs (produced from living sources) and radiopharmaceuticals (drugs with radioactivity) is Health Canada's Biologics and Genetic Therapies Directorate (BGTD)[104].

Regulatory Framework

Important laws, regulations and guidelines to be known are the: Food and Drugs Act (FDA)[105]; Food and Drug Regulations (FDR)[106]; Natural Health Products Regulations[107]; Guidelines for Good Clinical Practice[108]; Guidance for Clinical Trial Sponsors[109]; Medical Devices Regulations (SOR/98-282)[110].

Approval Process for Drugs

When a drug has successfully passed pre-clinical studies (in vivo or in vitro), a Clinical Trial Application (CTA)[111] to the HPFB – either the Therapeutic Products Directorate or the Biologics and Genetic Therapies Directorate - will be the next step in order to obtain approval for clinical trials conducted in humans.
Clinical trials involve three phases (I to III) in which, with an increasing number of volunteers, safety, efficacy and dose are being tested. The Submission of a CTA is a mandatory requirement for all phases of the clinical trials. As an Ethic Committee has to authorise the involved study material as well, Health Canada and the Public Health Agency of Canada's (PHAC) Research Ethics Board (REB)[112] provide relevant information which assists in the application procedure for this body. When all clinical trials' data are completed, a New Drug Submission (NDS)[113] may be forwarded for review to Health Canada (regular or fast track) in order to obtain market authorization. Documentation has to be presented to Health Canada in an electronic Common Technical document (eCTD) version.
For a generic drug, an **Abbreviated New Drug Submission** (ANDS)[114] providing all necessary information can be submitted in writing to Health Canada in order to apply for marketing approval. The documentation compares safety and effectivity of the generic pharmaceutical with the original drug.
An accelerated, fast track review process (**Priority Review**)[115] reduces the review procedure to 180 days instead of 300 days (normal procedure). It is intended for the treatment, prevention or diagnosis of serious, life-threatening or severely debilitating illnesses. Practitioners treating patients with serious or life-threatening conditions may obtain access, as an

[102] https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch.html
[103] https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/therapeutic-products-directorate.html
[104] https://www.canada.ca/en/health-canada/corporate/about-health-canada/branches-agencies/health-products-food-branch/biologics-genetic-therapies-directorate.html
[105] https://laws-lois.justice.gc.ca/eng/acts/f-27/
[106] https://laws.justice.gc.ca/eng/regulations/c.r.c., c. 870/index.html
[107] https://laws-lois.justice.gc.ca/PDF/SOR-2003-196.pdf
[108] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/international-conference-harmonisation/efficacy/good-clinical-practice-consolidated-guideline-topic.html
[109] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/clinical-trial-sponsors-applications.html
[110] https://laws-lois.justice.gc.ca/eng/regulations/sor-98-282/
[111] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/clinical-trials/applications.html
[112] https://www.canada.ca/en/health-canada/services/science-research/science-advice-decision-making/research-ethics-board.html
[113] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents/management-drug-submissions/industry.html
[114] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/announcements/notice-quality-chemistry-manufacturing-guidance-new-drug-submissions-ndss-abbreviated-new-drug-submissions.html
[115] https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/dhp-mps/alt_formats/hpfb-dgpsa/pdf/prodpharma/prfs_tpfd-eng.pdf

exception, to non-marketed drugs by means of the **Special Access Programme**[116] (SAP) - if conventional therapies have failed, are unsuitable, or unavailable. The SAP permits a manufacturer to sell a drug that cannot otherwise be sold or distributed in Canada. Additionally, all Canadian drug establishments must hold a **Drug Establishment Licence**[117] (DEL) to manufacture, package, label, distribute, import or test a drug. In order to obtain a DEL, applicants have to provide relevant information concerning their activities and each category of drug for which the license is requested.
In case of Health Canada's approval (Notice of Compliance), a **Drug Identification Number** (DIN)[118] will be allocated. The Sponsor may now start marketing the drug in Canada. Whilst a health product is approved and on the market, the Sponsor is obliged to ensure its continued compliance with the Food and Drug Regulations.
For more detailed information about drug product applications and submissions, please view relevant guidance documents[119].

Approval Process for Medical Devices

Medical devices are regulated by Health Canada's Medical Devices Bureau of the Therapeutic Products Directorate. According to the Canadian Medical Devices Regulations (CMDR) SOR/98-282, four Classes with an ascending risk (I, II, III or IV) exist.
As first step, the MD has to be classified[120].
For Class I devices, the Sponsor applies for a **Medical Device Establishment License** (MDEL)[121] and submits the MDEL application (in English or French). He provides the requested information and pays Health Canada fees. Approved Class I applications will be announced on the Health Canada website; MDEL certificate will be emailed accordingly.
For Class II – IV devices, a **Canadian Medical Device License** (MDL)[122] has to be applied for. The following documents have to be submitted in English or French: MDL application, Fee Form, labelling IFU (instructions for use), Declaration of Conformity, ISO 13485 MDSAP (Medical Device Single Audit Program) certificate.
For Classes III + IV: A **Premarket Review Document IMDRF ToC**[123] (International Medical Device Regulators Forum which has developed the Table of Contents formats for submissions in an electronic environment) is additionally required.
Health Canada reviews the documentation. In case of approval, licenses will be posted on the Health Canada website (plus a summary of decision for Class IV MDs), and a copy of the MDL will be sent by e-Mail to the Sponsor. The Medical Device may now be distributed in Canada. Registration of the license has to be renewed and annual fees must be paid to Health Canada; otherwise the license will be withdrawn.

For more detailed information, please view **Medical Devices Guidance Documents**[124]**.**

Regulatory Processes in Taiwan

Regulatory Environment

The **Taiwan Food and Drug Administration (TFDA)**[125] manages the regulatory system for food, drugs, medical devices and cosmetics and is the entry portal for the implementation of regulation, product registration and clinical trial approvals in Taiwan. Moreover, it supervises manufacturing and import of these products and is involved in safety surveillance on health

[116] https://www.canada.ca/en/health-canada/services/drugs-health-products/special-access/drugs.html
[117] https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences.html
[118] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/fact-sheets/drug-identification-number.html
[119] https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/applications-submissions/guidance-documents.html
[120] https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/guidance-document-guidance-risk-based-classification-system-non-vitro-diagnostic.html
[121] https://www.canada.ca/en/health-canada/services/drugs-health-products/compliance-enforcement/establishment-licences/directives-guidance-documents-policies/guidance-medical-device-establishment-licensing-medical-device-establishment-licence-fees-guide-0016.html
[122] https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/forms.html
[123] https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents/international-medical-device-regulators-forum.html
[124] https://www.canada.ca/en/health-canada/services/drugs-health-products/medical-devices/application-information/guidance-documents.html
[125] https://www.fda.gov.tw/ENG/

products. The TFDA is an administrative agency of Taiwan's **Ministry of Health and Welfare (MOHW)**[126]which had been formed in 1971 as the Department of Health and had changed to the MOHW in 2013. In addition, **the Center for Drug Evaluation (CDE)**[127], established by the Department of Health, supports the process of technical dossier reviews of drugs, APIs and medical devices.
Taiwan is a member of the **Pharmaceutical Inspection Convention Scheme (PIC/S)**[128]**,** an international cooperation which develops and implements harmonized Good Manufacturing Practice (GMP) standards and improves co-operation between regulatory authorities and pharmaceutical industry.

Legal Framework

The **1993 Pharmaceutical Affairs Act**[129] regulates the administration of pharmaceutical affairs including drugs, medical devices, pharmaceutical firms, pharmacies and others. The **Regulations for Governing the Management of Medical Device**[130] summarise the classification system (three classes, risk-based) for medical devices and state that the Manufacturing of MDs must be conform to the guidelines defined in the Good Manufacturing Practice for medical devices.
Moreover, the **Pharmaceutical Good Manufacturing Practice Regulations**[131] and the **Regulations for Registration of Medicinal Devices**[132] treating the registration of medical devices and the change, transfer, extension and reissuance of damaged or lost medical device permit licenses have to be named.

Approval Process for New Drug Applications (NDA)

The review and approval of new pharmaceuticals by the TFDA prior to marketing and is an obligatory process, which has to be carried out as follows:
The applicant submits the administrative and technical documentation to the CDE for review. An administrative reviewer conducts an initial assessment of the administrative documents. In case of a positive assessment result, a review team including experts in chemistry, pharmacology, pharmacokinetics, statistics and other domains will be formed for the technical documentation. During the continuous process, the sponsor may have to submit additional information. If necessary, the completed review report will be passed on to the Drug Advisory Committee for discussion. The Committee's statements will be included in the final review report. The administrative reviewer will then present the final review report for government officials' approval.

[126] https://www.mohw.gov.tw/np-108-2.html
[127] http://www.cde.org.tw/eng/
[128] https://www.picscheme.org/
[129] https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=L0030001
[130] https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=L0030054
[131] https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=L0030073
[132] https://law.moj.gov.tw/Eng/LawClass/LawAll.aspx?PCode=L0030055

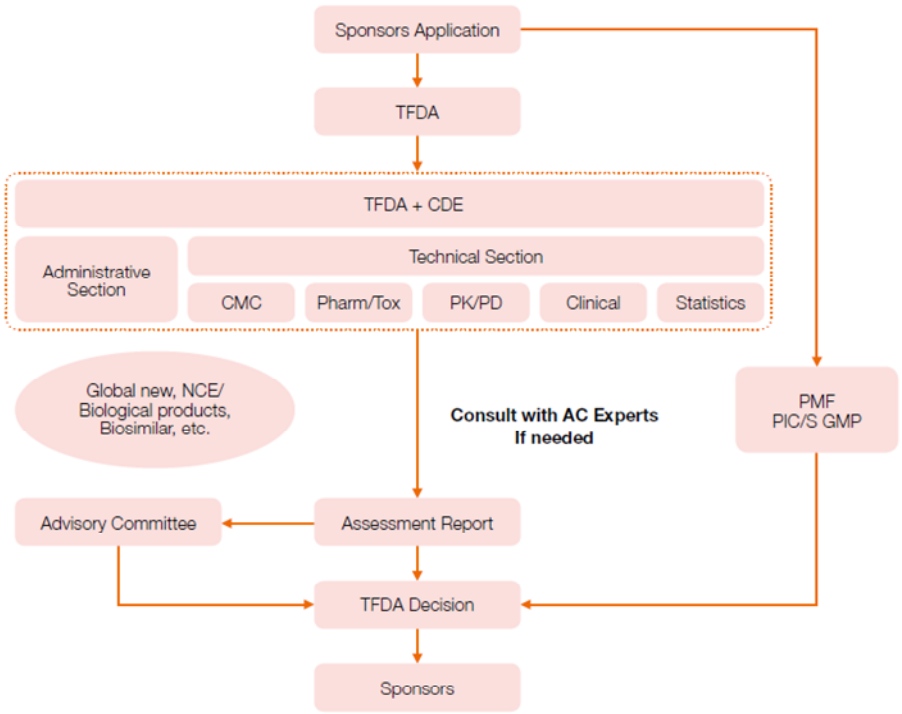


Figure 9: Approval Process for New Drug Applications[133]

Note:
CMC: chemistry, manufacturing and controls; PK: pharmacokinetics, PD: pharmacodynamics

Approval Process for Medical Devices

As first step, the MD has to be classified according to the system which consists of three classes: Class I (low risk, e. g.: stethoscopes), Class II (medium risk, e. g.: syringes, protein test systems) and Class III (high risk, e. g. pacemakers, plasma warming devices). Prior to being approved in Taiwan, all Class II and III MDs have to possess a marketing authorisation in their home country. Then a Taiwan Agent, with a legal office and a pharmaceutical sales license in Taiwan, has to be appointed in order to carry out the device registration and to operate on the applicants' behalf. Next, a ***Quality System Documentation (QSD)*** application, together with an ISO 13485 certificate, has to be submitted to the TFDA, and the QSD registration fee is to be settled. In case of a positive decision, the TFDA issues a QSD Approval Letter with a validity of three years.
For Classes II and III, the applicant has to obtain a ***Certificate of Free Sale (CFS)*** or ***Certificate to Foreign Government (CFG)*** in order to verify that his device possesses a sales authorisation for the country of his principle office.
As next step in the process, the applicant prepares and submits to the TFDA, for Class I MDs, a registration application including: a general product information (e. g.: labelling, the IFU (= instructions for use) document which has to be translated to Chinese and proof of QSD application. For Classes II and III, the registration application and dossier must be submitted, including the following documents: IFU (Chinese language), general information, QSD letter and product testing reports. Preclinical data may be required. Most testing conducted outside of Taiwan is usually accepted.
If MDs of Class I and II are already approved for sale in the US and Europe, they may follow a simplified application route without a review of preclinical testing results by TFDA. Application fees for all classes have to be paid. TFDA reviews the application. Novel (material or technology) medical devices or high Risk Medical Devices have to pass the TFDA Medical Device Committee Review and require clinical trial information which may add approximately eight months to the approval process.
If the MD is approved, TFDA releases a ***Medical Device Product License*** with a validity of five years. Renewal documents have to be presented six months prior to expiration. As final step, a licensed distributor has to appointed and an authorisation application filed by the Taiwan Agent for the product's import process. The applicant can start marketing his device in Taiwan

[133] https://www.pwc.tw/en/publications/assets/taiwan-health-industries.pdf, p 53

Concluding remarks

The overview of the regulation processes described above shall raise awareness of each producer of a new product for the healthcare system. Compliance of the product with the relevant regulation has to be checked right at the beginning of the product development process. Thereby it is important to understand that not only safety and efficacy are important issues, but that HTA and reimbursement become more and more important when it comes to the question of return on investment. Producers should seek early contact to the relevant agencies and ministries to make sure that the new product reaches the clinic or patient.

Annex 1

Entry Portal Reimbursement Institutes for Pharmaceuticals in Europe

Country	**Pharmaceutical Marketing Process**				**Public payers for medicines**	
	Market Authorisation	**Product Pricing**	**Reimbursement (outpatient)**	**Reimbursement (inpatient)**	**Outpatient**	**Inpatient** [a]
Austria	Medicines Agency	Ministry of Health	SHI	Hospitals and hospital owners (regions)	SHI (sickness funds, mainly at regional level)	Hospitals and hospital owners (mostly regions)
Belgium	Ministry of Health	Ministry of Economy/Economics	Ministry of Social Affairs	Ministry of Social Affairs	SHI	SHI
Cyprus	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	n/a	n/a
Czech Republic	Medicines Agency	Medicines Agency	Medicines Agency	Health insurance funds/Ministry of health	SHI	SHI
Denmark	Medicines Agency	No price regulation	Medicines Agency	Regions	Regions	Regions through a purchasing agency
Estonia	Medicines Agency	Ministry of Social Affairs [b]	Ministry of Social Affairs [b]	SHI	SHI	SHI
Finland	Medicines Agency	Ministry of Social Affairs and Health, Pharmaceutical Pricing Board	Ministry of Social Affairs and Health, Pharmaceutical Pricing Board	Hospitals	SHI	Hospital owners (municipalities)
France	Medicines Agency	Health Care Products Pricing Committee	SHI	SHI	SHI	Hospitals via their donation from the SHI and the SHI directly for expensive innovative medicines
Germany	Medicines Agency	Federal Joint Committee/SHI in negotiations with pharmaceutical company	Federal Joint Committee	Federal Joint Committee	SHI	SHI

Greece	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	SHI	Hospital budget for public hospitals
Hungary	Medicines Agency	Ministry of Health/ SHI	SHI/Ministry of Health	SHI/Ministry of Health	SHI	Hospitals
Ireland	Medicines Agency	Health Service Executive (competent authority for pricing and reimbursement decisions)	NHS	NHS	NHS	Hospitals via own budget/NHS for medicines covered under national drug management programmes
Italy	Medicines Agency	Medicines Agency	Medicines Agency	Medicines Agency	Regions	Regions
Latvia	Medicines Agency	NHS	NHS	NHS	NHS	NHS
Lithuania	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	National health insurance fund (SHI)	SHI, hospitals
Netherlands	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	SHI (health insurers)	SHI (health insurers)
Norway	Medicines Agency	Medicines Agency	Medicines Agency	Medicines Agency	National insurance scheme (SHI)	Regional health authorities (hospitals)
Poland	Medicines Agency	Ministry of Health	Ministry of Health/SHI	Ministry of Health/SHI	SHI	SHI
Portugal	Medicines Agency	Medicines Agency	Ministry of Health and Medicines Agency	Ministry of Health and Medicines Agency	NHS	NHS
Slovakia	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	SHI	SHI
Slovenia	Medicines Agency	Medicines Agency	SHI	SHI	SHI	SHI (only "expensive" medicines)
Spain	Medicines Agency	Ministry of Health/ Interministerial Committee for pricing	Ministry of Health	Ministry of Health	Autonomous community budgets	Autonomous community budgets
Sweden	Medicines Agency	Pricing and reimbursement agency	Pricing and reimbursement agency	Not defined	County councils (regions)	County councils (regions)
Switzerland	Medicines Agency	Ministry of Health	Ministry of Health	Ministry of Health	SHI	SHI
Turkey	Medicines Agency	Medicines Agency/ SHI	SHI	SHI	SHI	SHI
United Kingdom [c]	Medicines Agency	Department of Health [d]	Department of Health [d]	NHS England	NHS	NHS

Notes:

n/a = not available. SHI might be a single payer institution or different health insurers. Competences for pricing only refer to medicines under price control - usually reimbursable medicines

a: Public payers for inpatient medicines are, at first glance, the hospitals that procure, but they receive funding from other institutions (e.g.: their owners).

b: In 2018 the Ministry of Social Affairs was renamed the Health Insurance Fund.

c: Information refers to England only.

d: In 2018 the Department of Health was renamed the Department of Health and Social Care.

List of Medicines Agencies: https://www.ema.europa.eu/en/partners-networks/eu-partners/eu-member-states/national-competent-authorities-human
List of Ministries of Health: https://www.gfmer.ch/Medical_search/Ministry_health.html

Source: WHO - "Medicines Reimbursement Policies in Europe" (2018)

Annex 2

Pricing & Reimbursement of Medical Devices (MD) in Europe

Reimbursement of Medical Devices in Europe

Country	Payment		Legal Frame			Evaluation		Technical Assistance		Remark
Austria	Sickness funds (3 categories = 9 regional sickness funds for each state	9 State Health funds (LGF) = regional funds distributing money to funds hospitals	Federal Ministry of Labor, Social Affairs Health and Consumer Protection	Federal Health Commission (Bundesge-sundheits-kommission)	Austrian Medical Chamber	Ludwig Boltzmann Institute HTA (LBI-HTA)	Austrian Health Institute (GÖG)	LKF Working Group of Federal Health Commission		Austrian hospitals receive a global budget, using a diagnosis-related group (DRG) system.
Denmark	5 Regional Health Authorities	98 Local Health Authorities (Municipalities)	Danish Health Authority (Sundhedsstyrelsen)			Danish Regions	Hospital and regional HTA Units	Danish Health Data Authority (Sundheds-datastyrelsen)		Hospitals are financed in a combination of block grant (80%) and DRG-based (20%) funding.
Estonia	Estonian Health Insurance Fund (Haigekassa; EHIF)	Health Board (Terviseamet)	The Government (Valitsus)	Ministry of Social Affairs (Sotsiaal-ministerium; MoSA)		Nat. Institute for Health Development (Tervise Arengu Instituut; NIHD	Estonian Medical Association (Eesti Arstide Liit; EMA)	NordCase (Entity main-taining the NordDRG system)	Health and Welfare Information Systems Centre (TEHIK)	Combination of DRG and fee for service model for reimbursement of hospital services. Estonia shares the DRG system (NordDRG) with other Nordic countries.

Finland	311 Municipalities (local level)	Social Insurance Institution of Finland (KELA)	Ministry of Health and Social Affairs	20 Hospital Districts	5 Catchment areas (specific University Hospitals)	National HTA Coordination Unit (FINCCHTA)		Nordic Casemix Centre (Collaboration on DRG system)	The National Institute of Health and Welfare (THL)	Finland is divided into 20 hospital districts that are independent in the selection of payment model.
France	General statutory health insurance scheme	Agricultural statutory health ins.; and scheme for self-employed people (RSI)	National Union of Health Insurance Funds (UNCAM)	Ministry of Health		National Authority for Health (HAS)		Technical Agency for Information on Hospitalisations (ATIH)		Reimbursement is very complex and has high evidence requirements. Excellent coverage opportunities for innovation funding, telemedicine etc..
Germany	Sickness funds		Federal Ministry of Health (BMG)	Federal Joint Commit- tee (G-BA)	National Association of Statutory Health Insurance Funds (GKV-Spitzen-verband)	Institute for Quality and Efficiency in Healthcare (IQWIG)		Institute for the Hospital Remuneration System (InEK)	German Institute of Medical Documentation and Information DIMDI)	Hospital care (except capital equipment) is funded via DRGs. Innovative expensive devices and procedures can benefit of NUB (innovation funding).
Greece	National Organisation for the Provision of Health Services (EOPYY)		National Organisation for the Provision of Health Services (EOPYY)	Ministry of Health		Central Health Council (KESY)		The Greek DRG Institute (KE.TE.K.N.Y)		Greece uses DRG system to reimburse services provided in hospital care. A new DRG

										system (based on the German model) will be implemented soon.
Hungary	State Secretariat Of Health (Ministry of Health)	National Health Insurance fund of Hungary (NEAK)	State Secretariat Of Health (Ministry of Health)			Technology Assessment Dept. at the Nat. Instit. Of Pharmacy + Nutrition	Medical Professional College	State Health Supplementary Center		Hospital procedures are typically financed using the DRG system
Italy	Local health firms (ASLs)		Ministry of Health	Regions; State-Regions Conference	Cabina di Regia (Steering Committee for HTA)	Nat. HTA organisation AGENAS; Nat. HTA center within Sup. Health Insti-tute (ISS)	Regional Technical Commission for Medical Devices	Ministry of Health		Funding at hospital level is performed using a global budget or DRGs. Lack of structured processes leads to a very complex and long market access.
Netherlands	Insurance companies		Ministry of Health, Welfare and Sport	Dutch Health-care Authority (NZa)	Dutch Health-care Institute (Zorginstitute Nederland)			Dutch Health-care Authority (Nza)		Hospital procedures are reimbursed via the DRG system, mostly negotiated between hospitals + insurance companies.

Norway	Regional Health Authorities	Norwegian Health Economics Administration (Helfo)	Ministry of Health and Care Services	Norwegian Directorate for Health	Ordering and Decision Forums of "New Methods" framework	Norwegian Institute of Public Health (NIPH)		Norwegian Directorate for Health; Norweg. Directorate for eHealth	Nordic Casemix Center (Nordic collaboration on DRG system)	DRG based model contributes up to 50% of all revenue of hospitals in Norway.
Poland	National Health Fund (NFZ) with 16 regional branches		Ministry of Health (MoH)			Agency of HTA and Tariffication (AOTMiT)		Agency of HTA and Tariffication (AOTMiT)		System includes two types of DRGs, several add-on reimbursement categories and highly specialised care.
Portugal	NHS Portugal (= SNS; universal)	Health Sub-systems (20% of the population)	Ministry of Health	Directorate-General for Health (DGS)		National Authority of Medicines & Health Products (Infarmed)		Central Administration of the Health System (ACSS)	National Health Observatory (OPSS)	Hospitals are primarily funded using a global budget principle with adjustment using a DRG system.
Spain		Health Ministries of ACs (autonomous communities)	Ministry of Health, Consumption and Social Welfare	Health Ministries of ACs (autonomous communities)	Inter Territorial Council of SNS (Consejo Interterritorial)	Commission of Benefits, Assurance and Financing	Spanish Network of Agencies for the Evaluation of Health Techn. + Benefits			Hospitals are mainly financed via a global budget principle. There is no reimbursement system in practise.
Sweden	County Councils and Regions		National Board of Health and Welfare	Regional Priority Councils	Healthcare regions	Swedish Council on Technology Assessment in Healthcare (SBU)	Dental + Pharmaceutical Benefits Agency (TLV); Regional HTA units	Swedish Association of Local Authorities and Regions (SALAR)	National Board of Health and Welfare; Nordic Casemix Center	Regions select payment model for hospital care. In most regions, it is a global budget

										approach. Sometimes, an activity-based funding according to NordDRG is used.
Switzerland	Health Insurance Companies		Federal Office for Public Health (FOPH)			Swiss Conference of the Cantonal Ministers of Public Health (GDK/CDS)	Swiss Association of Hospitals (H+); Comm. of medical tariffs (MTK/ CTM)	German Institute of Medical Documentation and Information (DIMDI)	Federal Statistical Office (BFS/UFS)	Swiss DRG model (SwissDRG) includes 100% of hospital admission. It is based on the German DRG system and adjusted to Swiss conditions.
Turkey	Social Security Institution (SSI)	Ministry of Treasury and Finance	Ministry of Health (MoH)			Reimbursement Commission	Health Technology Assessment Department	Department of Health Statistics		Complex, inflexible reimbursement system which generally does not provide revision of national reimbursement prices for procedures and devices.
UK(England)	NHS England (national commissioner)	209 Clinical Commissioning Groups; NHS Public Health	NHS Public Health commissions screening programs)	NHS England	Dept. of Health (collects Reference Cost = foundation of tariff calcul.)	National Institute for Health + Care Excellence (NICE)	Accelerated Access Collaborative	NHS Digital	NHS Improvement	Complex reimbursement system (National Tariff Payment System) and funding framework with a strong

										consultant role of NICE.

Adapted to :Source: "2020 European MedTech + IVD Reimbursement Consulting Ltd."