HAUTE AUTORITÉ DE SANTÉ

Pathway of medical devices in France

Practical guide

November 2017

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can be downloaded at **www.has-sante.fr**

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Abbreviations and acronyms

ACB	Actual clinical benefit
ACV	Added clinical value
AIMD	Active implantable medical device
ANSM	French National Agency for Medicines and Health Products
CAV	Clinical added value
CCAM	Joint classification of medical procedures
CEESP	Commission for Economic and Public Health Evaluation
CEPS	French Healthcare Products Pricing Committee
CI	Clinical investigation
CME	Health Care Organisation Medical Committee
CNEDiMTS	Medical Device and Health Technology Evaluation Committee
DEMESP	Medical, Economic and Public Health Assessment Division
DRG	Diagnosis related group
ED	Early Dialogue
EU	European Union
EUDAMED	European Database on Medical Devices
FSSC	French Social Security Code
HAS	French National Authority for Health [Haute Autorité de santé]
HPG	Homogeneous patient group
ICER	Incremental cost-effectiveness ratio
IMD	Implantable medical device
IVDMD	*In vitro* diagnostic medical device
LNE/G-Med	National Laboratory for Metrology and Testing in the Medical Health Field
LPPR	List of products and services qualifying for reimbursement
MD	Medical device
NB	Notified body
PHC	Public Health Code
SPL	Sale price limit
PMCF	Post-marketing clinical follow-up
PSUR	Periodic Safety Update Report
QMS	Quality management system
SDC	Summary of device characteristics
SEAP	Professional Procedures Assessment Department
SED	Medical Device Assessment Department
SEESP	Department for Economic and Public Health Assessment
TC	Transparency Committee
TR	*Tarif de responsabilité*
UDI	Device identification system
UDI-ID	Unique device identifier
UDI-PI	Device production identifier
UNCAM	National Association of Health Insurance Funds

Preface

Regardless of its focuses (assessment of health technologies, definition of good professional practices, certification, etc.) and the audiences it addresses (public authorities, healthcare professionals, manufacturers, etc.), Haute Autorité de santé (HAS) [the French National Authority for Health] is at the service of citizens, users of the health system and patients. Ultimately, all actions undertaken by HAS are guided by the usefulness for those who receive care.

The CNEDiMTS is therefore particularly committed to ensuring that patients and people with disabilities can benefit as quickly as possible from clinical and technological advances in Medical Devices.

In its task of assessing the relevance of reimbursement of a Medical Device (MD) by the community, the CNEDiMTS focuses on promoting access of patients and healthcare professionals to useful and safe innovation.

In fact, the CNEDiMTS feels it is important that manufacturers, researchers and healthcare professionals working on a project know the pathway of MDs in France. While the CE marking of an MD allows its free circulation in Europe, the devices reimbursed by the community are specific to each member state.

By making stakeholders aware of the regulatory prerequisites and challenges of relevant clinical development (which is the purpose of this document), the CNEDiMTS wishes to be part of this constructive dynamic to improve the assessment of medical devices. While European Regulation 2017/745 states the clinical requirements for manufacturers to obtain CE marking, the CNEDiMTS's assessment is carried out according to other criteria, defined by French law.

However, if all of the expectations of the different steps of a MD assessment are taken into consideration from the beginning of clinical development of the MD, time and resources will be saved for the benefit of all, and especially patients and people with disabilities.

Happy reading

I. Adenot

Chair, CNEDiMTS

Introduction

According to the Economic, Social and Environmental Committee, in 2015, 800,000 to 2,000,000 medical devices (MDs) were available in France (1). There is a great heterogeneity among these devices, both in the intended use of the product and the associated level of risk.

The number of MDs reimbursed is constantly increasing. In 2015, their reimbursements reached EUR 8.7 billion, with an increase of about 2.8% compared to 2014 (2).

However, a lack of clarity regarding the pathway to follow in France to make an MD available to patients is regrettable.

Facilitating the access of patients or people with disabilities to these technologies is a major concern for HAS. In this context, HAS has implemented support measures for manufacturers, such as early dialogues and pre-submission meetings. This guide, which aims to help manufacturers better understand the regulatory prerequisites and the challenges of relevant clinical development, is also part of these measures.

The continuous evolution of the industry means information has to be updated regularly, and so this is the third update of the MD practical guide by HAS. This update is all the more important since European Regulation 2017/745 (3), implemented on 26 May 2017, will become mandatory for all new devices as from May 2020. It will replace the guidelines on MDs [Directive 93/42/EEC (4)] and AIMDs (active implantable medical devices) [Directive 90/385/EEC (5)]. It should be noted that European Regulation 2017/745 states the clinical requirements for manufacturers to obtain CE marking: demonstration of conformity with general safety and performance requirements includes a clinical assessment.

All requirements concerning clinical assessments, those of the European regulation and those for an application for reimbursement by national solidarity scheme, should be taken into consideration from the beginning of clinical development to save time and resources and to provide all the necessary items for the successive assessments of the medical device.

This guide follows the chronological pathway of an MD development:

- assessment for **marketing**;
- assessment for **reimbursement** and **pricing** principles in France;
- a focus on the challenges of **clinical development** with its key concepts prior to the application for reimbursement;
- **clinical follow-up** after marketing and after reimbursement.

This guide aims to describe the market access conditions as provided for in Regulation 2017/745 implemented on 26 May 2017. Nevertheless, this guide is not a guide for application of new European Regulation 2017/745. It only contains part of it in terms of the continuum of assessment in the life cycle of an MD. Manufacturers should use this text now to prepare for compliance with Regulation 2017/745. European and national communications will support them throughout the transitional period.

1. Marketing

Before undertaking development of a product, it is important to precisely determine its status, based on the available regulatory definitions (e.g. cosmetic, medicinal product, medical device (MD[1]), tissues or cells of origin animal, etc.). This status will determine the regulations with which the product must comply.

European Regulation 2017/745, which will permanently replace Directives 93/42/EEC (4) and 90/385/EEC (5) in 2020, defines a medical device as “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.”

This definition again emphasises **the significant heterogeneity** of the MD industry, including devices as diverse as dressings, eyeglasses, pacemakers and medical imaging devices.

Changes made by the regulation:

The definition of an MD stated in Regulation 2017/745 has been extended compared to prior directives on MDs and explicitly includes the medical purpose.
The scope of application of the regulation has been specified. In addition to MDs, it applies to their accessories and products without medical purpose, namely for aesthetic purpose, listed in Annex XVI of the regulation.

Note:

Application of European Regulation 2017/745 will become mandatory on 26 May 2020 and Directives 93/42/EEC and 90/385/EEC will be repealed with the exception of a few provisions. A transition period has been established until this date, in which manufacturers can therefore choose a CE marking procedure according to Directives 93/42/EEC and 90/385/EEC or Regulation 2017/745. Certificates issued under the directives by a notified body will remain valid until their expiration date, at most 5 years after issue and no later than 27 May 2024. The devices may continue to be marketed or used until 27 May 2025.

1.1 CE marking

To be marketed in the European Union, an MD must **comply with the general safety and performance requirements** applicable to it. These requirements depend on different criteria, including the intended use of the MD and its risk class. They are stated in Annex I of Regulation 2017/745 for MDs and active implantable MDs (AIMDs). *In vitro* diagnostic MDs (IVDMDs) are covered by Regulation 2017/746 (6); elements specific to this regulation will not be covered in this guide.

It is up to a **notified body**[2] (NB) **chosen by the manufacturer** to carry out the assessment[3] of this conformity (except for certain class I MDs, where this responsibility falls on the manufacturer). Once conformity has been demonstrated, manufacturers may establish the EU declaration of conformity and affix the CE marking of conformity.

[1] To simplify reading of this guide, the term MD includes active implantable medical devices (AIMD)
[2] Articles 35 to 50 of European Regulation 2017/745
[3] Articles 52 to 55 of European Regulation 2017/745

MDs can be marketed only if the **CE marking has previously been affixed under the responsibility of the manufacturer**[4] (this does not apply to MDs for clinical research or "custom-made" MDs) and the manufacturer has drawn up the **EU declaration of conformity**[5].

Note:

Each EU country has one or more competent authorities for the safety of health products. In France, the French National Agency for Medicines and Health Products (ANSM) is in charge of device market surveillance and is responsible for designation and monitoring of the notified bodies (NBs) within its territory. Multiple NBs may be designated in the same country; these NBs may have specific areas of competence.

A manufacturer is free to choose the NB that it wishes, provided that the MD to be assessed falls within the field of competence of the body.

Changes made by the regulation:

Notified bodies will be designated based on reinforced criteria, in particular as regards clinical competence, with joint assessment of several European experts.

▶ Risk class of the device

Determining the risk class of an MD is essential. It will determine the steps to take to obtain CE marking, in particular the choice of assessment procedure and the clinical requirements necessary.

MDs are divided into four classes: class I, class IIa, class IIb and class III[6] based on their **level of risk** (Table 1).

Table 1. Classification of medical devices based on risk[7]

Class	Level of risk
Class I	Low degree of risk
Class IIa	Moderate degree of risk
Class IIb	High potential of risk
Class III	Very serious potential of risk

The rules for determining the class of the MD are listed in Annex VIII of Regulation 2017/745 and take into account the duration of use, the invasive or non-invasive nature and the type of invasiveness, the possibility (or not) of reuse, the therapeutic or diagnostic aim, and the part of the body concerned.

Non-sterile class I MDs or those without a measuring function are self-certified by the manufacturer. For other devices, the intervention of a notified body is mandatory for the CE certification process.

Changes made by the regulation:

The number of rules and classification criteria was expanded (22 rules and 80 criteria instead of 18 rules and 56 criteria).

For example, software is the subject of a classification rule.

▶ Identification of the device

Changes made by the regulation:

This complete section is a new part of the regulation.

[4] Articles 20 and 56 of European Regulation 2017/745
[5] Article 19 of European Regulation 2017/745
[6] Classification rules defined in Annex VIII of European Regulation 2017/745.
[7] Article 51 of European Regulation 2017/745

The identification and traceability of MDs are reinforced through the creation of a unique device identification system (UDI system). Each MD will have a unique identifier, if applicable, for each packaging. The UDI is composed of:

- **a unique device identifier (UDI-ID)** specific to a device model
- **a UDI production identifier (UDI-PI)** specific to a medical device production unit

Note:

The affixing of UDI carriers on the label and on all higher packaging levels, will come into effect on different dates, based on the risk class:

- Implantable and class III MDs: 26 May 2021
- Classes IIa and IIb: 26 May 2023
- Class I: 26 May 2025

For reusable MDs, the UDI support must be affixed on the device itself.

Manufacturers are responsible for the initial introduction and updating of identification data and other data elements concerning the device in the UDI database[8].

▶ Choice of assessment procedure

The assessment procedures to obtain CE marking vary **based on the risk class and characteristics specific** to certain products. These procedures include both an audit of the manufacturer's quality management system (QMS) (except for some class I devices) and an inspection of technical documentation (TD) of the devices by the NB (see Figure 1).

Two QMS assessment methods (QMS1 and QMS2) are possible. Article 52 of Regulation 2017/745 further specifies these procedures.

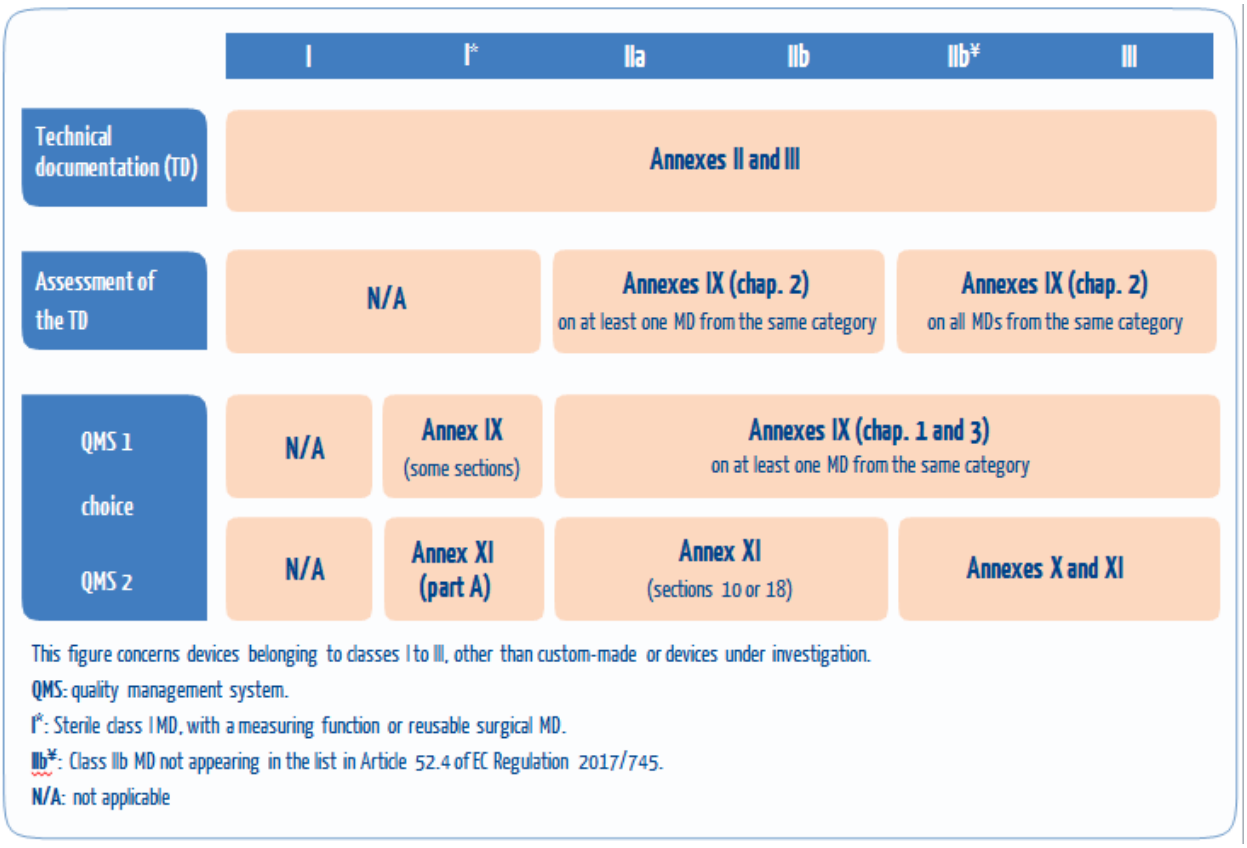

Figure 1. Procedures for assessment of conformity based on the class of medical device

[8] Annex III, Part C - Article 5.2 of European Regulation 2017/745

For MDs that are not the subject of harmonised standards or for which the existing standards are insufficient or in case of public health concern, the European Commission may define common specifications for these devices. These specifications will be able to define supplemental requirements in terms of safety, performance, technical documentation, clinical assessment, post-marketing clinical follow-up (PMCF) or clinical research[9].

Changes made by the regulation:

The constituent elements of the technical documentation are specified (see Annex II of Regulation 2017/745). Moreover, the quality management system now includes **clinical assessment and post-marketing clinical follow-up (PMCF)**. A clinical assessment plan must be established prior to the clinical assessment (see Annex XIV – 1a of Regulation 2017/745).

Common specifications defining additional requirements may be implemented for certain devices.

▶ Clinical requirements for CE marking

Regulation 2017/745 reinforces the requirements for clinical assessment. In particular, it includes the **phase of collection of clinical data** already available in the literature as well as the **implementation of any clinical investigations** (also called clinical trials) that may be necessary. In a limited number of situations, it is possible to appeal to the notion of "equivalence" [10].

▶ Clinical assessment

The manufacturer is responsible for planning, performing and documenting a clinical assessment. It **specifies and justifies the level of clinical evidence necessary** to demonstrate conformity with the safety and performance requirements of the regulation, which depend on the characteristics of the device and its intended purpose.

The clinical assessment of the MD must follow a defined procedure methodologically based on **critical assessment of the relevant scientific literature**, **the results of all available clinical investigations** and **consideration of alternative treatment options** currently available.

Regulation 2017/745 requires the manufacturer to have a **post-marketing surveillance plan,** so that knowledge about the MD can be updated throughout its life cycle. This surveillance plan must in particular include a **post-marketing clinical follow-up** (PMCF), which is a continuous process that updates the clinical assessment through which the manufacturer proactively collects and assesses clinical data (already mandatory since March 2010).

For some MDs (see below), it will be necessary to conduct a clinical investigation to obtain CE marking.

▶ Clinical investigation

Regulation 2017/745 specifies that, in the case of implantable devices and class III devices, clinical investigations (CIs) **must be conducted**, **unless the three following criteria are met**:

- the device has been designed by modifying a device already marketed by **the same manufacturer**;
- equivalence with this device has been demonstrated and approved by the NB;
- the clinical assessment of the currently marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

[9] Article 9 of European Regulation 2017/745
[10] Article 61 of European Regulation 2017/745

Additional exceptions:

The manufacturer of an MD demonstrated to be **equivalent** to an already marketed device **not manufactured by it** may also rely on the 3 criteria mentioned above in order not to perform a clinical investigation, provided that the following conditions are also met:

- the two manufacturers have a contract in place that explicitly allows the manufacturer of the second device full access to the technical documentation on an ongoing basis, and
- the original clinical assessment has been performed in compliance with the requirements of this Regulation, and the manufacturer of the second device provides clear evidence thereof to the notified body.

Note:

While clinical investigations implemented to obtain CE marking are primarily conducted to demonstrate the performance and safety of a device, expected clinical investigations for reimbursement and pricing must also answer the question of the role of the device in the available arsenal (therapeutic, diagnostic or compensation for disability). To save time, it is therefore important for a manufacturer to anticipate in its clinical development programme, before marketing, expectations for:

- obtaining CE marking;

- access to reimbursement, if applicable.

► Notion of equivalence

It is important to properly understand the notion of **device equivalent** to another device. Two devices are considered equivalent if it is possible to simultaneously verify[11]:

- **clinical** equivalence (intended use, site in the body, population, etc.);
- **technical** equivalence (specifications, properties, set-up, etc.);
- **biological** equivalence (biocompatibility, tissues, materials, etc.).

The characteristics listed above must be similar to the extent that there would be no clinically significant difference in the safety and clinical performance of the device. Considerations of equivalence are based on proper scientific justification. It must be clearly demonstrated that manufacturers have **sufficient access to the data relating to devices** that they consider equivalent in order to justify their claims of equivalence.

Changes made by the regulation:

Clinical assessment is one of the most reworked elements in the regulation.

Requirements related to clinical investigations are now more precise via Article 62 and Annex XV. Other than the exceptions listed above, implantable MDs and class III MDs must undergo clinical investigations in order to obtain CE marking.

Obligations concerning equivalence of MDs are reinforced.

For all class III devices and for class IIb devices intended to administer/eliminate a medicinal product into or from the body, the manufacturer may, before carrying out its clinical assessment and/or clinical investigation, consult a group of European experts.

[11] Annex XIV-A-3 of the European Regulation 2017/745

▶ Summary of device characteristics

In France, since 1 July 2017[12], manufacturers or authorisation holders of implantable MDs and class III MDs – except for custom-made MDs – must electronically submit to ANSM a summary of device characteristics (SDC).

The information to be included in the SDC are specified in Article R.5211-66-1 of the Public Health Code (elements of identification, of use, of description and of clinical assessment of the MD).

This same obligation appears in Article 32 of Regulation 2017/745.

Article 32 of Regulation 2017/745 establishes that manufacturers produce a summary of safety and clinical performance characteristics for implantable devices and for class III devices. The SDC will be validated by the NB. It is intended for the user/patient of the device and will be made available to the public via Eudamed.

Changes made by the regulation:

In the regulation, the SDC is a component of the technical dossier sent to the NB. It will be intended to be communicated to the public by Eudamed (European Database on Medical Devices); thus, it will be written so as to be comprehensible by patients.

1.2 ANSM missions

The French National Agency for Medicines and Health Products (ANSM) is involved in certain steps prior to and after the CE marking but does not directly take part in the review of the CE marking application (which falls under the competence of the NBs).

▶ Clinical trials

ANSM is involved in the phase of clinical trials conducted in France through the assessment and authorisation of research involving human subjects.

European Regulation 2017/745 will bring the rules into line with the rules that will come into effect in application of the European regulation on clinical trials of medicinal products (7).

▶ Notified bodies

ANSM, as a competent authority, is in charge of assessing, **designating** and **monitoring** notified bodies in France. To date, only the Group for Assessment of Medical Devices (G-Med) of the National Laboratory for Metrology and Testing in the Medical Health Field (LNE/G-Med) is a notified body in France for MD and IVDMD directives.

▶ Market surveillance

ANSM is the competent authority responsible for market surveillance. To this effect, it can, in particular, monitor technical documentation, carry out inspections (announced and unexpected) and pronounce sanitary policy measures for compliance or prohibition of marketing.

ANSM must be kept informed (by the manufacturer or its representative) of the arrival on the market of any new **MD or AIMD of class IIa, IIb or III** to allow for possible verification of conformity. All data that makes it possible to identify these devices, as well as a copy of the labelling and instructions, must be sent[13].

When the manufacture of an MD involves a product of animal origin, the manufacturer must specify this to ANSM, as well as the species of origin.

[12] Decree no. 2016-1716 of 13/12/2016 on the summary of medical device characteristics, published in the Official Journal of the French Republic on 15/12/2016. http://www.legifrance.gouv.fr/ [consulted on 02/10/2017].
[13] Articles L.5211-4 and R.5211-66 of the Public Health Code, which transpose Article 14 of European Directive 93/42/EEC of 14 June 1993

In addition, any manufacturer whose **corporate headquarters is in France** and who markets for the first time in France or in any other member state of the European Union a **custom-made or class I MD** must report this medical device to ANSM[14].

> More information is available in the ANSM document: Guidelines for Entrepreneurs Developing a Medical Device/*In Vitro* Diagnostic Medical Device.

Article 29.4 of Regulation 2017/745 establishes that prior to marketing a device other than a custom-made device, the manufacturer will register in the European Eudamed database a certain amount of information about its device, as stated in Annex VI.

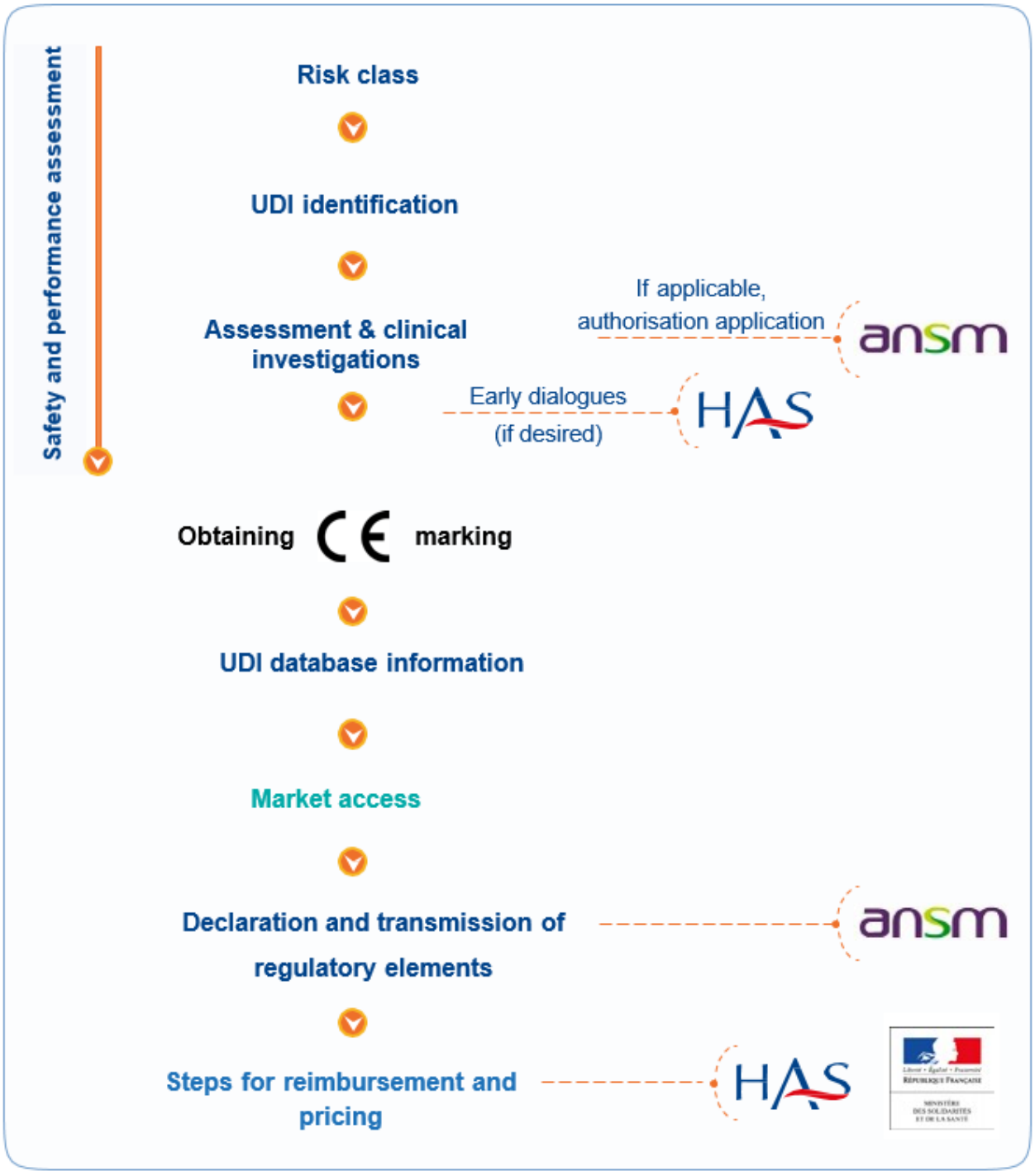

Figure 2. Simplified steps to market access*

[14] Article R.5211-65 of the Public Health Code

*The modifications established by Regulation 2017/745 will be implemented gradually and will be obligatory on 26 May 2020.

2. Steps for reimbursement and pricing in France

2.1 Preamble

After obtaining CE marking, the MD may be marketed on the European market. This step does not imply its automatic reimbursement by the national solidarity scheme of a member state, in this case France. For this, additional procedures must be carried out.

For reimbursement by the national solidarity scheme, data related to the clinical benefit and role in the therapeutic strategy are expected.

The reimbursement methods determine the assessment circuit for reimbursement.

The information provided about the application for reimbursement and pricing described apply to MDs, AIMDs and IVDMDs.

2.2 Different reimbursement arrangements

There are different reimbursement arrangements for medical devices and they depend, among other factors, on the conditions of use of the device.

In an ambulatory setting, MDs for individual use at the patient's home (outside of any context of hospitalisation) may be reimbursed through their inclusion in the LPPR, while those related to a procedure performed by a healthcare professional are included in the tariff of the procedure. When used for or during the performance of a professional procedure, MDs used outside of any context of hospitalisation are not subject to individualised pricing; they are valued through the procedure. This procedure is included in the joint classification of medical procedures (CCAM).

MDs used at **healthcare organisations** are primarily reimbursed through diagnosis related groups (DRGs), except for certain MDs reimbursed outside of DRGs (they are in this case included in the list of products and services reimbursed in addition to hospital service, more commonly known as the "additional list"[15]).

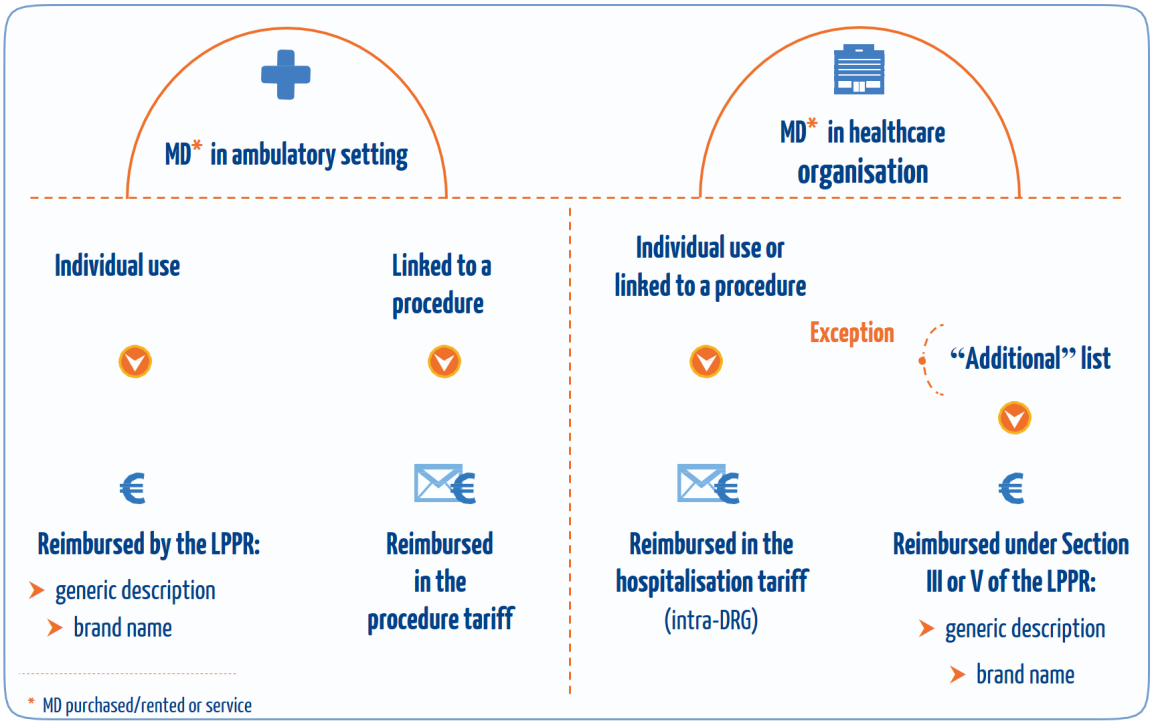

Figure 3. Reimbursement arrangements for medical devices: ambulatory/healthcare organisation

[15] Article L.162-22-7. The additional list can be found at: http://www.atih.sante.fr/dispositifs-medicaux-pris-en-charge-en-sus [consulted on 04/09/2017]

▶ Reimbursement by diagnosis related groups (DRGs)

This reimbursement arrangement only involves healthcare organisations. Since 2005, the latter have been financed within the framework **tarification à l'activité (T2A)**, a fee-for-service pricing system in which expenditures on most MDs are directly integrated into hospital service. Thus, in 2017, MDs such as lens implants and osteosynthesis implants were included in the cost of diagnosis-related groups (DRGs).

For most MDs, no specific assessment is carried out for reimbursement of devices via DRGs. It is up to the Health Care Organisation Medical Committees (CMEs) of public healthcare organisations or organisation medical conferences of private healthcare organisations to create the list of sterile devices that the organisation plans to use[16]. The tariff of the MD is then negotiated directly with each purchaser or hospital purchasing group.

► "Positive" intra-DRG list

A specific assessment of certain categories of MDs appeared to be necessary. The Law of 2011, reinforcing the health safety of medicine and health products, also introduced the possibility of including certain homogeneous categories of MDs on a positive list. This provision determines not only the reimbursement for these products, but also their purchase, supply and use by the healthcare organisations.

In application of this provision, a decree from the Ministry of Health[17] was published. It concerns 4 categories of MDs.

Table 2. Homogeneous categories of health products submitted to the positive list by decree[17]

Description	Method of inclusion
Intracranial stents used in angioplasty of atherosclerotic stenoses	Brand name
Conventional implantable cardiac defibrillators: with intracavitary lead (single, double and triple chamber)	Generic description
Implantable cardiac defibrillators without intracavitary lead (single, double and triple chamber)	Brand name
Biological surgical heart valves	Brand name

If the device belongs to one of these categories, manufacturers, their representatives or distributors involved must submit an application for inclusion on this intra-DRG list with the Medical Device and Health Technology Evaluation Committee (CNEDiMTS). These MDs must then meet, considering their invasiveness or the risks they may pose to human health, at least one of the following requirements[18]:

- validation of their clinical effectiveness,
- definition of particular technical specifications,
- assessment of their efficiency compared with available therapeutic alternatives.

This inclusion is given for a fixed term, which is renewable, and may be subject to conditions of prescription and use or subject to the completion, by the manufacturers (or their authorised representatives) or distributors, of additional studies requested on the products concerned.[18]

▶ Reimbursement through the LPPR

The LPPR[19] is the list of products and services qualifying for reimbursement by the French health insurance scheme. It allows reimbursement of MDs for individual use in an ambulatory setting or of some devices, reimbursed outside of DRGs, in healthcare organisations (see the box below about the "additional" list).

This list **relates to the medical device itself** (e.g. a hearing aid) and also the service necessary for its proper use (e.g. service of a hearing aid specialist to adjust and set the hearing aid for a patient). This complementarity between the device and the service is one of the characteristics of the LPPR.

[16] Article R.6111-10 of the Public Health Code
[17] Decree of 29 January 2016, modifying the modified Decree of 28 November 2013, establishing for the year 2013 the homogeneous categories of health products mentioned in Articles L.165-11 and R.165-49 of the French Social Security Code
[18] Article L.165-11 of the French Social Security Code
[19] Article L.165-1 of the French Social Security Code

It is divided into five parts:

- **Section I:** MDs for treatments at home, living aids, dietary products and dressings
- **Section II:** Orthotics and prostheses
- **Section III:** Implantable medical devices, implants and tissue grafts of human origin
- **Section IV:** Vehicles for physically-handicapped people
- **Section V:** Invasive medical devices not eligible under Section III of the LPPR

Creation of Section V:

Until 2015, the LPPR was reserved for MDs used in an ambulatory setting and for MDs implanted or present in the body for more than 30 days.

In 2015, Section V of the LPPR was created (see Decree of 4 May 2017 published in the official journal of 6 May 2017) to allow the inclusion on the LPPR of invasive devices not eligible under Section III that meet the following two criteria:

- **invasive nature**: those that partially or fully penetrate the interior of the body, either through an orifice of the body or through the surface of the body;
- **placement criteria**: those that can only be used by a physician.

The purpose of Section V is to be able to reimburse certain invasive devices used as part of a procedure performed by a physician and not meeting the criteria of Section III.

If the manufacturer or distributor of an MD for individual use wants it to be reimbursed by the French health insurance scheme, they must submit an application for inclusion of their MD on the LPPR. Inclusion can either be under the **generic description** of all or part of the product in question, or under a **brand name**. It is up to the manufacturer or distributor to initiate the application for reimbursement.

Manufacturers or distributors **are required to declare to ANSM** all products or services that they market and include on the LPPR, specifying the corresponding inclusion code. They are also required to report any modification affecting the code of a product or of a service previously reported[20,21].

► Inclusion as a generic description is the general principle

This inclusion arrangement identifies a type of product according to its indications and its technical specifications, without mentioning brand name or company name. If a product or service is compliant with the description and minimal technical specifications of an already existing generic description included on the LPPR, it is sufficient for the manufacturer, or the distributor, to label its product according to the LPPR nomenclature as defined in the Decree of 26 June 2003[22], and to make the declaration of inclusion to ANSM with the corresponding code. **This inclusion is the responsibility of the manufacturer or distributor.**

In this case, the product does not undergo an assessment by the Medical Device and Health Technology Evaluation Committee (CNEDiMTS) during inclusion. Generic descriptions have a **maximum duration of 10 years, which is renewable**[23,24].

○ *Enhanced generic description*

In 2015, the enhanced generic description was introduced among the arrangements for inclusion of MDs on the LPPR, with the aim of both strengthening health safety and reducing expenditures unduly borne by the French health insurance scheme[25]. In 2017, this provision has not yet been used.

[20] Article L.165-5 of the French Social Security Code
[21] Article 11 of Law no 2008-337 of 15 April 2008
[22] Decree of 26 June 2003 on the coding of the list of products and services qualifying for reimbursement under Article L. 165-1 of the French Social Security Code
[23] Decree 2004-1419 of 23 December 2004
[24] The Decree temporarily extends the duration of validity of the inclusion of products and services included under generic description until 31 July 2015.
[25] Decree 2015-1649 of 11 December 2015

► The inclusion can be done under brand name or trade name

In some cases, inclusion under a generic description is not possible. The alternative is then **inclusion under brand name** or trade name. This is the case, in particular[26]:

- for a product of an **innovative nature** (according to Article R.165-3 of the French Social Security Code (FSSC));
- for a **unique product** and/or one which does not allow a generic description to be drawn up;
- to ensure **follow-up of a device** when required by the impact on the French health insurance scheme expenditures, by public health needs or by the monitoring of minimal technical specifications.

In other cases, inclusion on the LPPR is carried out under a generic description which is the default inclusion choice.

Inclusion by brand name requires submitting a reimbursement application dossier to the Ministry of Health and simultaneously sending a copy of the dossier to the CNEDiMTS[27]. The CNEDiMTS assesses the merit of this application based in particular on the reimbursement application dossier submitted by the company (manufacturer or distributor). In case of favourable opinion for reimbursement, the MD reimbursement tariff is then negotiated between the French Healthcare Products Pricing Committee (CEPS) and the company.

The inclusion under brand name is intended to be temporary[28]. As soon as a competitor appears for the innovative product (inclusion by brand name of an MD of the same class), inclusion using a generic description may seem justified. On the other hand, when inclusion using the brand name is done for public health reasons, it is included *a priori* for the long term.

Exceptions from the principle of inclusion on the LPPR are possible, in particular for certain custom-made devices or in the case of certain patients with rare diseases or chronic conditions.

[26] Framework Agreement of 16 December 2011 between the CEPS and the professional organisations affected by the products and services included on the LPPR
[27] Article R.165-7 of the French Social Security Code
[28] Article R.165-3 of the French Social Security Code "(...) At any time, inclusion using a generic description can be substituted for inclusion of one or more products using the brand or trade name by decree of the Minister of Social Security and the Minister of Health after the Medical Device and Health Technology Evaluation Committee has given its opinion."

“Additional” list in healthcare organisations:

The principle of the *tarification T2A* involves flat-rate pricing for care. The expenditures for most MDs are thus directly integrated into the hospital services (DRGs). **As an exception**, and in order to support and distribute innovation **in healthcare organisations**, some MDs likely to introduce a heterogeneity in the cost of hospitalisation due to their variable prescription within the same DRG may be **reimbursed in addition** to the hospital services tariff. These devices are then included on a list, called the “additional” list (see Article L. 162-22-7 of the French Social Security Code).

Inclusion on the additional list is a decision of the Minister of Health after the CNEDiMTS has given its opinion. To be included on this list, the products must also be included on the LPPR in Section III or V.

Inclusion of or refusal to include MDs on the additional list in a therapeutic indication that has been the subject of an opinion by the CNEDiMTS will be examined by the Ministry with regard to the following elements:

- expected use of the MD in the therapeutic indications considered;
- actual clinical benefit (ACB) level
- clinical added value (CAV) level
- estimated frequency of placement within homogeneous patient groups (HPGs)
  - a frequency of use below 20% in the HPGs favours inclusion on the additional list;
- estimated cost of the device(s) considering associated MDs in relation to the tariff of the hospitalisation service;
  - an MD tariff greater than 30% of the tariff in a DRG favours inclusion on the additional list;
- application of the principle of equal treatment with regard to existing comparators in the indication involved.

MDs reimbursed by Section V are, by nature, reimbursed in addition to the professional procedure. A demonstration of the superiority of these devices compared to the other devices is therefore expected. For example, a minor (IV) or non-existent (V) CAV for these MDs does not allow inclusion on the additional list unless the comparator is a Section V MD already included on the additional list.

The procedure to apply for inclusion of a product or service on the additional list is described on the website of the Ministry of Solidarities and Health (www.solidarites-sante.gouv.fr).

The figure below summarises the general process for inclusion of an MD on the LPPR.

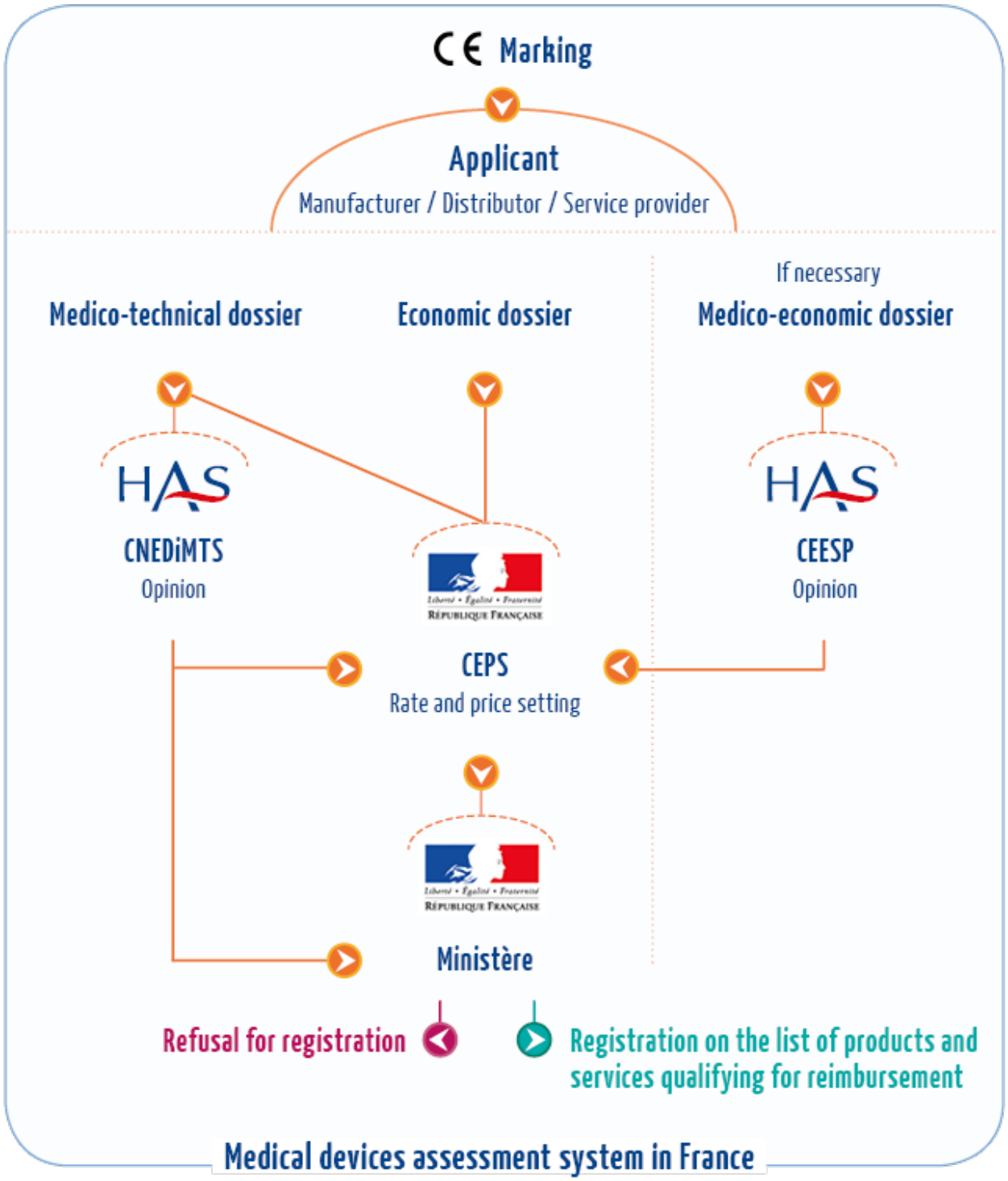

Figure 4. Inclusion of a medical device on the LPPR

▶ Reimbursement as part of a professional procedure

A “professional procedure” is a category of health technologies that involves any clinical or technical action performed by a healthcare professional[29] with the aim of diagnosis, prevention, treatment or rehabilitation.

[29] Physician/surgeon, medical biologist, surgeon-dentist, midwife, physiotherapist, nurse, etc.

Based on the situations, the professional procedure may involve the use of MDs for individual or collective use or also medicinal products.

Some MDs for individual use, used for or during the realisation of a procedure by healthcare professionals and whose action is not carried out beyond the medical procedure, are reimbursed through these professional procedures.

When no procedure on the CCAM corresponds to the action using the MD, the CNEDiMTS on its own initiative proceeds with the assessment of the procedure at the same time as the assessment of the device.

▶ *Innovation Pass*

Principle:

The Innovation Pass allows the **exceptional and temporary reimbursement of an innovative MD or procedure subject to the achievement of a study** to provide missing clinical or medico-economic data (8). This exceptional reimbursement is a decision, made after receiving the opinion of HAS, by the Minister of Health through publication of a specific decree. As it is an exceptional reimbursement, its implementation implies the selection of the technologies likely to benefit from it.

Reimbursement may be partial or full. The objective is to promote the implementation of a decisive clinical study to allow the reimbursement of the MD according to the “pay to see” principle (contrary to common law: “see to pay”). Determination of the flat fee takes into account the duration of the study as well as the time necessary for the assessment and pricing of the product.

The Ministry of Health monitors the progress of the study.

Eligibility criteria are based on the **innovative** nature of the technology and on the **relevance of the clinical or medico-economic study** proposed. Compliance with these criteria is assessed by the HAS Board and the Ministry of Health.

Further information about the Innovation Pass, in particular eligibility criteria (9) and procedures for submitting[30] the dossier (with HAS and the Ministry of Health) and applications for early dialogues (10), can be found on the HAS website (www.has-sante.fr).

Four important points to emphasise:

- the application dossier is based on the first available data;
- the eligibility criteria imply that these data support the technology;
- the proposed study protocol is an integral part of the application dossier;
- the applicant for the Innovation Pass is also the sponsor of the study.

[30] Article R.165-66 of the French Social Security Code

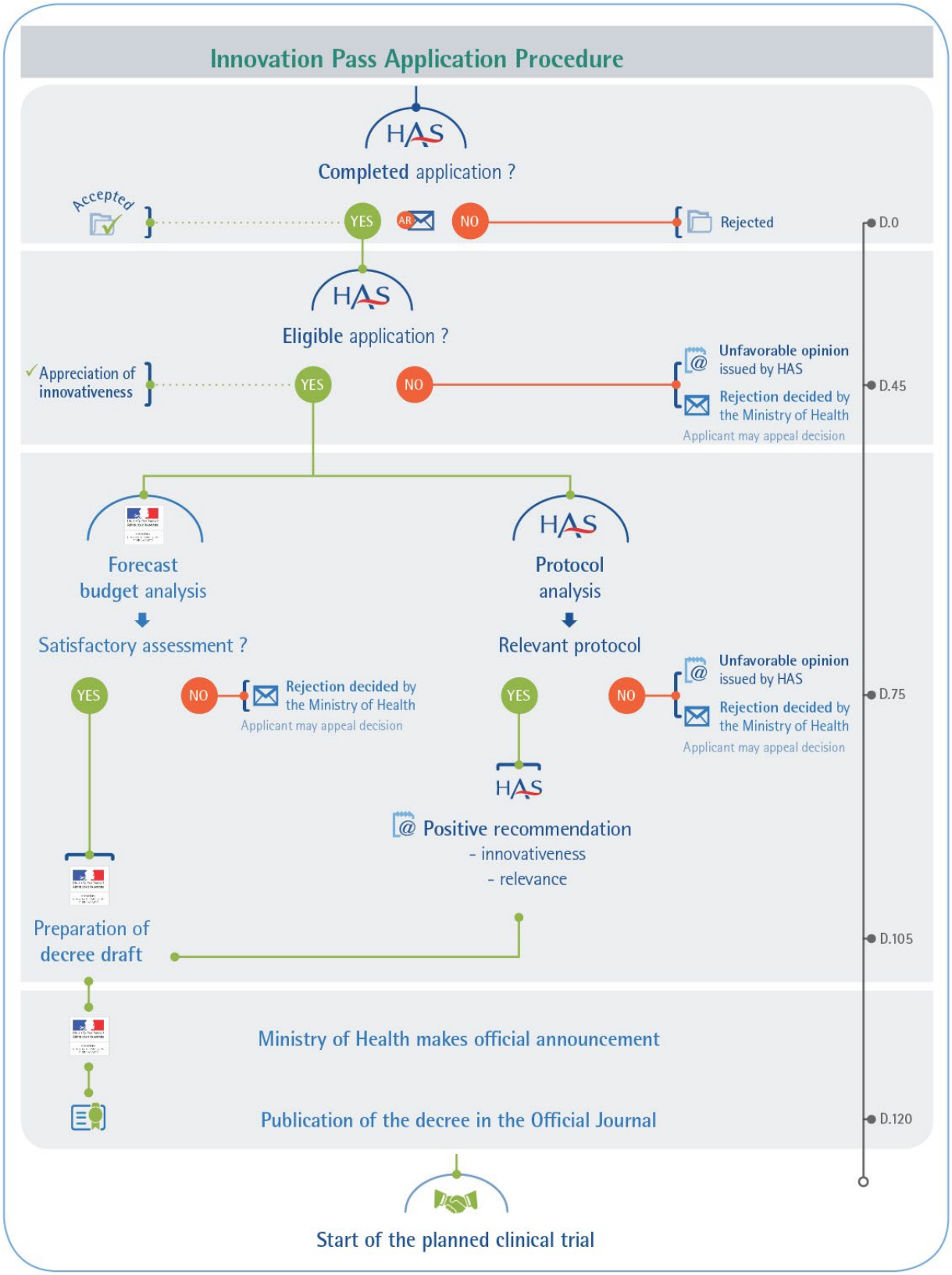

Figure 5. Innovation Pass application procedure (11)

2.3 Medico-technical assessment of the CNEDiMTS

The medico-technical assessment of the CNEDiMTS **only** involves devices within the scope of the LPPR and devices on the so-called “intra-DRG” list.

Note:

While clinical investigations implemented with the objective of obtaining CE marking are primarily conducted to demonstrate the performance and safety of a device, expected clinical investigations for reimbursement must also answer the question of the role of the device in the therapeutic strategy and allow its added value to be determined compared to the available arsenal.

▶ Medical Device and Health Technology Evaluation Committee (CNEDiMTS)

The CNEDiMTS is the HAS committee that assesses, with a view to their reimbursement by the French health insurance scheme and their correct use, MDs and health technologies, including those reimbursed in the context of hospital services (see Internal regulations of the CNEDiMTS) (12).

The CNEDiMTS is comprised of (12):

- 21 full members with voting rights: 20 with scientific or technical expertise in the domain of health products and services (specialist physicians, nurses, occupational therapists, pharmacists, etc.) and one representative of a patient and user association; and 7 substitute members.
- 8 members with an advisory vote: representatives of the directorates of the Ministry of Health, ANSM and the 3 main French health insurance schemes.

Within HAS, the Medical Device Assessment Department (SED) and the Professional Procedures Assessment Department (SEAP) support the CNEDiMTS in its missions and ensure the internal expertise of all topics examined.

Each dossier or topic studied by the SED or SEAP is the subject of a deliberation and a vote at a meeting of the CNEDiMTS. The opinions and recommendations are thus based on the principle of collegiality.

Three types of activity are carried out (13):

- assessment of MD reimbursement application dossiers (under brand name or on intra-DRG list) with delivery of opinion;
- assessment of homogeneous categories of products, in particular generic descriptions;
- assessment of health technologies (not medicinal products).

▶ Medico-technical opinion

The medico-technical assessment is prepared by the SED for the members of the CNEDiMTS on application of the manufacturer. This application can be of different natures. It may correspond to inclusion of an MD on the LPPR or, when the MD has already been included once, a modification of the conditions of inclusion or a renewal of the inclusion of the device.

The principles of assessment of medical devices by the CNEDiMTS have been published and are available on the HAS website (14).

In the case of an initial application for inclusion or renewal of inclusion, the Committee’s opinion relates in particular to the assessment of the **actual clinical benefit (ACB)** and, if the latter is sufficient, to the assessment of the **clinical added value (CAV)**.

Considering that patients have specific knowledge about their disease, HAS has developed the following ways to involve patients in the medico-technical assessment (15):

- the opportunity given to patient associations to submit a “patient contribution” on an MD (in the context of submission of an application dossier for inclusion under brand name);
- stakeholder hearings.

► Application for inclusion on the LPPR

○ *Assessment of actual clinical benefit*

Actual clinical benefit (ACB) is a clinical service. It is assessed **in each of the indications of the product** or service and, if applicable, by population group. The assessment of the ACB is based on two criteria defined in Article R.165-2 of the French Social Security Code[31]:

- **the benefit of the product** with regard to its therapeutic or diagnostic effect or its effect in compensating for disability, as well as its adverse effects or risks related to its use and its role in the therapeutic strategy considering other available therapies;
- **its expected public health benefit**, in particular its impact on the health of the population, in terms of mortality, morbidity and quality of life, its ability to meet a therapeutic need with regard to the severity of the condition or disability, its impact on the healthcare system and on public health policies or programmes.

The ACB is assessed, if appropriate, based on the technical specifications and specific conditions of prescription and use to which the inclusion is subject.

Products or services whose actual clinical benefit is insufficient are not included for reimbursement.

○ *Assessment of clinical added value*

When the ACB is sufficient to justify inclusion for reimbursement, the CNEDiMTS must also deliver an opinion on “the assessment of the clinical added value (CAV) compared to a comparable product, procedure or service or to a group of comparable procedures, products or services, precisely designated, considered as standard according to the current data of science and subject or not to reimbursement[32]”.

This assessment leads the CAV to be considered major (I), important (II), moderate (III), minor (IV) or absent (V). It is conducted for each therapeutic or diagnostic indication or indication for compensation of disability in which the Committee deems the inclusion justified. The CAV is one of the criteria used by the CEPS to determine the tariff of a device.

Note:

In the case of a **medico-technical assessment of an MD included on the “intra-DRG” list, the CAV is not assessed**.

[31] Article R.165-2 of the French Social Security Code
[32] Article R.165-11 of the French Social Security Code

Figure 6. Assessment of clinical added value by the CNEDiMTS when the actual clinical benefit is sufficient

For the same category of MDs, the levels of CAV assigned by the CNEDiMTS evolve with regard to the available arsenal and the acquisition of new data. As a general rule, in the case of an application for inclusion of a MD from a category of products not yet assessed, the CAV is granted **in relation to the existing therapeutic or diagnostic strategy or strategy for compensation of a disability**.

In its opinion, the Committee may also specify the additional studies necessary for assessment of the actual clinical benefit, or its clinical added value, which should be submitted at the time of renewal of inclusion.

► Renewal of inclusion

Inclusion of a product included under the brand name is granted for a maximum of 5 years. Its ACB and CAV are then re-assessed periodically. Inclusion of the product can only be renewed if the product or service has a sufficient ACB to justify continuing its reimbursement.

The actual clinical benefit (ACB) is determined by re-assessment of the criteria that led to the assessment of the ACB determined at the previous assessment, taking into account new data available (new clinical studies, new international guidelines, other products and services included since, data from the post-inclusion study requested if applicable, etc.). The assessment of the ACB is carried out in each of the indications initially submitted for reimbursement.

When the ACB is sufficient to justify renewal of inclusion, the assessment of the clinical added value (CAV) compared to the comparator, considered standard according to current data, is carried out.

In the case of **generic** descriptions, the reviews carried out by the CNEDiMTS re-assess the **justification for maintaining their inclusion based on the criteria mentioned above and, if necessary, specify their technical specifications, their indications and define their methods of use**.

2.4 Medico-economic assessment of the CEESP

The medico-economic assessment only involves certain applications for inclusion on the LPPR.

▶ Commission for Economic and Public Health Evaluation (CEESP)

To ensure the sustainability of the health system largely based on collective management of health care expenditures, choices about the allocation of resources must be made. The Commission for Economic and Public Health Evaluation (CEESP) of HAS was created to ensure that the **measurement of the benefit for society of a strategy or a product** is taken into account in decisions about strategies or products, and in particular decisions about their price (16). The CEESP relies mainly on the work of the HAS Department for Economic and Public Health Assessment (SEESP).

The **measurement of the benefit, for society, of a new strategy or a product, compared to the existing strategy or product**, is established by comparison of the resources used (costs) with the results obtained, which allows the efficiency to be assessed. This analysis makes it possible to adequately articulate public health objectives and the resources that are dedicated to it.

The CEESP takes a stance and develops opinions and recommendations based on a number of scientifically established grounds and elements. The efficiency opinions of the CEESP are intended for the CEPS. The opinions of the CEESP concerning assessments of public health and health technologies are validated by the HAS Board. These opinions are joined with the opinions of the two medico-technical committees of HAS, namely the Transparency Committee (TC) for medicinal products and the CNEDiMTS for medical devices. The CEESP is *in fine* responsible for the scientific validity, methodology and ethical quality of the work of HAS in matters of economic assessment and assessment of public health actions and programmes (see 2016 activity report) (17).

▶ Efficiency opinion

A medico-economic assessment is required when an MD claims a CAV of I to III and is likely to have a significant impact on the French health insurance scheme expenditures[33,34].

The impact on the French health insurance scheme expenditures is qualified as significant:

- when the manufacturer claims, for its product, an impact on the organisation of care, professional practices or patient care conditions;
- in the absence of such claim, when the annual revenue from the product, all indications combined, is greater than or equal to EUR 20 million incl. tax (the second full year of marketing).

The HAS Board ensures application of the terms of the decree and does not require an economic assessment when a conventional low-cost procedure is planned or when the product patent is in the public domain (see 2016 activity report) (17).

When a medico-economic assessment is required, the manufacturer must create an economic assessment dossier which presents the context of the application, the data used as well as the explanation of the structuring choices of the assessment, the modelling parameters and the results obtained, according to the methodological guidelines established by HAS (18).

[33] Decree no. 2012-1116 of 2 October 2012 on the medico-economic missions of the Haute Autorité de santé
[34] Decision no. 2013.0111/DC/SEESP of 18 September 2013 of the HAS Board on the significant impact on Health Insurance expenditures triggering the medico-economic assessment of products claiming a CAV of level I, II or III

The CEESP then delivers an opinion about the foreseeable or observed efficiency of reimbursement of the health product or technology by the French health insurance scheme.

The opinion is based on:

- the comparative analysis, between the different relevant therapeutic alternatives;
- the ratio between the costs incurred and the expected or observed benefits for health;
- the quality of life of the people involved.

Additional information about the content of the efficiency opinion and its appendices are available in the HAS document "efficiency opinion format" (19) available on the HAS website (www.has-sante.fr).

► Conclusion of the CEESP

The conclusion of the Committee relates in particular to the methodological conformity of the medico-economic model submitted (assessed with regard to the determining factors mentioned above and further explained in the methodological guide). In case of methodological non-conformity, the CEESP rules on the nonconforming nature of the study due to major reservations and considers the results of the study submitted to be unusable. Thus, no quantitative results are included in its conclusion and it is specified that the efficiency cannot be assessed.

When the study method is considered acceptable, the CEESP specifies:

- the incremental cost-effectiveness ratio (ICER) of the product or average net profit to interpret the result;
- the nature of any methodological reservations;
- the assessment of the level of uncertainty characterising the results and the main sources of uncertainty;
- elements allowing assessment of the impact of a price variation on the ICER.

> **Note:**
>
> To help public decision-making and to negotiate prices, the CEESP may be required to comment on the high nature of the ICER. However, at this stage, no reference value has been defined to consider an ICER "too" high.

The final efficiency opinion issued by the CEESP is primarily intended for the CEPS for negotiation of pricing. It is made public on the HAS website (www.has-sante.fr).

A methodological guide (20) for manufacturers was created by HAS. It aims to explain the reference framework for economic assessment by presenting the principles and methods used to carry out and analyse these assessments.

Manufacturers can supplement the efficiency dossier with an analysis of the budgetary impact of the introduction of their product onto the market. The format and methodological prerequisites have also been published by HAS (18).

2.5 HAS support

Before submitting a dossier, communication between applicants and HAS departments is recommended. This communication can take place in various ways depending on the state of progress of the dossier.

► Early dialogues

For devices in clinical development – including before obtaining CE marking – the HAS Medical, Economic and Public Health Assessment Division (DEMESP) has implemented the opportunity for early dialogues (EDs) (21).

The company or developer can request an ED focused on questions related to the **clinical development of the health product** in question or a joint ED also covering questions related to conducting a medico-economic study, if an assessment of the product's efficiency is planned.

The EDs organised by HAS are optional, non-binding, confidential and free.

No member of the CNEDiMTS participates in these meetings.

The answers provided by the HAS departments to companies or developers during these EDs are in no way an assessment and do not prejudice the conclusions that may result from the assessment by the Committees involved, namely the CNEDiMTS and, where applicable, the CEESP (if submitting an economic assessment dossier).

► ED for products in clinical development

The objective of these EDs is to provide answers to questions posed by companies or developers on **how they can conduct clinical trials** to be able to provide data that meet the requirements of the assessment for reimbursement and price.

The implementation of such a dialogue is only useful for products that are in clinical development:

- once the protocol plan is established;
- before starting the clinical study.

No member of the CNEDiMTS participates in these meetings.

For these EDs, refer to the document dedicated to medical devices: “Early dialogue with HAS for a medical device in clinical development - MD methods for submission and proceedings” available on the HAS website (www.has-sante.fr).

► ED before submitting a medico-economic study

To promote the conformity of economic studies submitted with HAS guidelines, the manufacturer is offered the opportunity to request an early dialogue with the SEESP. This dialogue allows the manufacturer to **present to HAS the main methodological choices** it is leaning towards to structure its economic study, and to **share methodological questions that have arisen**.

No member of the CEESP participates in these meetings.

The answers provided by the SEESP do not commit the Committee as regards the opinions it will deliver when assessing the dossier submitted by the manufacturer.

For these EDs, refer to the document: "ED economic dossier" available on the HAS website (www.has-sante.fr).

For devices requesting dialogues with SEESP and SED concomitantly, there will be a collaboration between these two departments.

► Pre-submission meeting

Manufacturers or service providers and home equipment distributors who want to receive **clarification about the technical and regulatory aspects necessary for creation of the medico-technical dossier** can request a pre-submission meeting (22).

These dialogues are organised by HAS (on request) before the submission of a dossier for inclusion on the LPPR.

This type of meeting cannot lead to advice in terms of company strategy. They are optional, non-binding, confidential and free.

These meetings are different from early dialogues, which focus on methodological elements related to the development of the device.

2.6 Pricing of medical devices included on the LPPR

▶ The French Healthcare Products Pricing Committee

The French Healthcare Products Pricing Committee (CEPS), an **inter-ministerial body** placed under the joint authority of the Ministries of Health and Economics, is primarily tasked by law with setting the prices of medicinal products and tariffs of medical devices for individual use reimbursed by the compulsory French health insurance scheme (23).

The decisions of the CEPS are made in a collegial manner, in accordance with the guidance it receives publicly from the ministers, and under the supervision of the administrative judge. The prices or tariffs are preferably set by means of **agreements** concluded with the companies marketing the products or, for some MDs, with the representative professional organisations of these companies.

The CEPS also contributes, through its proposals, to defining economic policy for health products.

The CEPS is tasked with proposing the reimbursement tariffs of products and services included on the LPPR and, if appropriate, their price. It may, in setting these tariffs and prices, conclude agreements with the manufacturers and/or distributors involved regarding sale volumes or the conducting of a post-inclusion study.

▶ Setting the *tarif de responsabilité* and price

The CEPS concluded, in 2011, a framework agreement[26] with the professional organisations affected by the products and services included on the LPPR.

***Tarif de responsabilité* (TR):** The *tarif de responsabilité* is the tariff on which French social security reimbursement is based.

***Prix limite de vente (PLV)* [Sale price limit]:** This is the maximum price that the public can be charged for a product.

The difference between the PLV and the TR is thus paid by the patient or falls under the private insurance system.

In most cases, the TR and the PLV are identical, so there is no amount to be paid for patients who have supplemental insurance.

The **determination of tariffs primarily takes into account**[35]:

- the CAV;
- if applicable, the results of the medico-economic assessment of tariffs of comparable products or services;
- planned or observed sale volumes;
- planned or observed amounts reimbursed by the compulsory French health insurance scheme;
- anticipated and actual conditions of use.

Note:

A significant amount of information can be found by reading the framework agreement mentioned above, especially about: post-inclusion studies, pricing principles (volume price clauses, consideration of innovation, etc.).

The pricing of procedures included on the joint classification of medical procedures (CCAM) is not negotiated with the CEPS but with the National Association of Health Insurance Funds (UNCAM).

The figure below shows the main steps of reimbursement and pricing applications.

[35] Articles L.165-2 and R.165-14 of the French Social Security Code

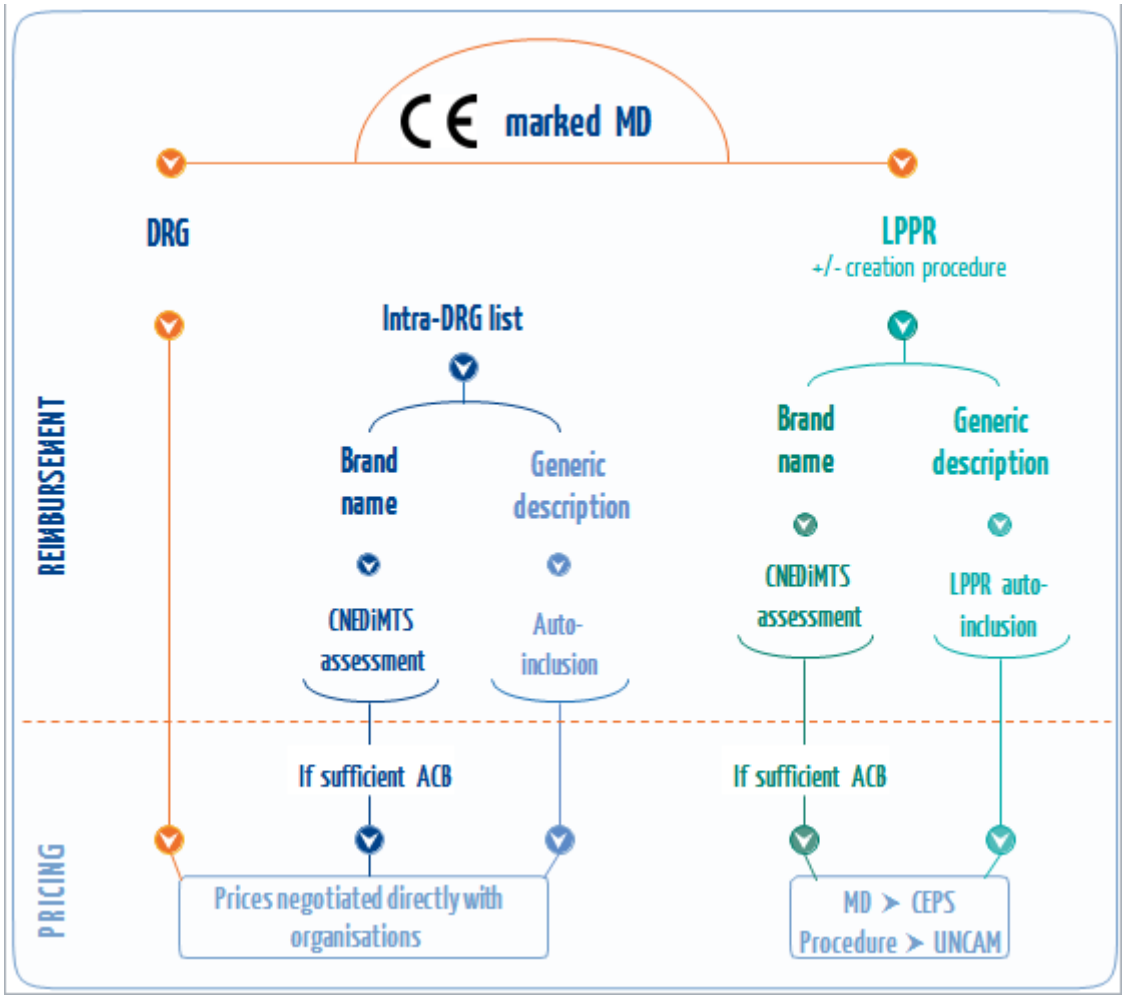

Figure 7. Simplified pathway of steps to take for reimbursement and pricing

3. Challenges of clinical development

3.1 Key stages in clinical development

Clinical development and optimisation of prototypes are crucial stages for a new MD.

These stages must be prepared as early as possible. Anticipating these stages enables relevant clinical studies to be proposed that demonstrate the benefit of this new MD and will eventually optimise its valorisation. Conducting a quality clinical study is an opportunity to show the interest of the new MD both with respect to patients and to obtain reimbursement. To improve the readability of the guide, the decision was made to group sick people and people with disabilities under a single term (patient).

It is important to **identify from the outset, through systematic research, the clinical data that are already available, or in progress, within the domain of the new MD** or the reference strategy in question as well as any recommendations.

- The **preclinical phase** includes not only the **technological development** but also the implementation of ***in vitro* tests** and sometimes **animal experiments**.
- The **clinical phases** include feasibility and development studies (safety and performance), as well as studies demonstrating the clinical benefit. The implementation of a **protocolised** collection of clinical data from the first patient is an asset for the distribution of a new technology. The existence of a protocol and the quality of this collection are determining factors.

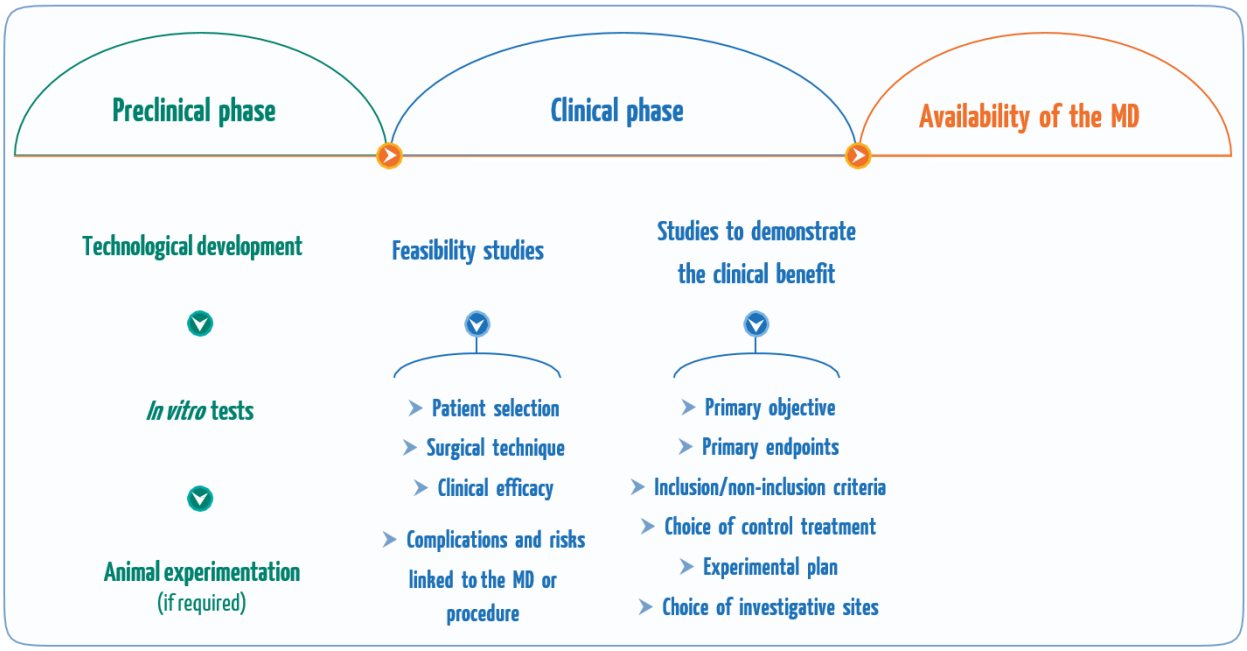

Figure 8. Key stages in clinical development

Throughout the clinical development of an MD, some specific characteristics must be taken into account, namely:

- the **product status** based, for example, on whether or not it is combined with a medicinal product;
- the **life cycle** which can be very short due to rapid technical progress;
- the **lifetime**, which depends on the obsolescence of the MD or, if applicable, the duration of implantation;
- the **technical performance** (to be separated from the clinical benefit);
- the **clinical benefit**, which can depend not only on the MD itself, but also on the performance of the medical team (operator-dependent nature, learning curve) and the technical facilities;
- the **target population** affected by the MD, which may sometimes be small.

▶ Feasibility studies

Depending on the type of MD, they are proposed immediately following the pre-clinical phase or in parallel with industrial development. Generally, the methodologically appropriate type of study at this stage is a non-comparative prospective study.

The results of feasibility studies may, in particular, provide elements to:

- determine the effect size that will be used to design future studies;
- estimate the number of patients necessary for future trials.

Depending on the context, one or more studies are necessary to answer different questions, in particular:

- the type of patients who will benefit from the new MD;
- the development of the surgical technique, in particular implantation;
- the clinical efficacy;
- the complications and risks associated with the MD and the implantation technique.

▶ Selecting patients who will benefit from a new MD

This stage makes it possible to **specify the clinical forms of the condition** in which the new device would bring about the expected therapeutic efficacy in the patients.

It must also specify the characteristics of the patients (age, sex, acceptable comorbidities) **which would have the least possible effect on the result, in order to select a sufficiently homogeneous group of patients for future studies**.

However, even at this early stage of development, a choice must be made, which is often delicate, between a very narrow selection of patients that could optimise the amplitude of the observed effect, and a wider selection that would optimise recruitment conditions and the possibility of generalising the study results.

▶ Development of the surgical technique, in particular implantation

One or more studies are necessary to develop the implantation technique of a new MD and **to describe the different surgical steps, the technical facilities and the personnel** necessary for the success of the procedure.

At the end of this stage, actual **specifications** are established to **standardise** the technique as well as possible. They include the description of the procedure and necessary resources. They facilitate implementation of the next stage for demonstration of clinical benefit.

▶ Complications and risks

Two types of adverse events may be reported:

- those **linked directly to the MD**;
- those that are **related to the implantation or surgical technique**.

At this stage, the objective of the studies is to identify the main complications. This estimate is essential for establishing the future risk/benefit ratio.

▶ Studies to demonstrate the clinical benefit

The design of the trials essential to demonstrating the clinical benefit of the new MD must **be based on the different feasibility and development studies**.

Depending on the challenges, the trials chosen may be superiority, equivalence or non-inferiority trials.

The type of trial with the best level of evidence to demonstrate the clinical superiority of a new MD over the reference strategy is the randomised, controlled clinical trial. This type of trial, when it can be conducted and when it is well designed, optimally enhances a new MD. The randomised, controlled trial can also be used to show equivalence or non-inferiority of the MD.

The randomised, controlled trial, in addition to having to fulfil standard methodological criteria, must also be clinically relevant. When drawing up the study protocol, particular attention must be paid to a certain number of points, presented below.

These various points must be systematically addressed and the **questions must be asked when developing any trial to demonstrate the clinical benefit of a new MD**. This **systematic approach** allows the creation of a trial that will best show the interest of the new MD. It is possible that this trial, depending on the specific **characteristics of the MD**, cannot be controlled and randomised. In this case, the people conducting the project can use other experimental plans suitable to the context: the systematic approach then makes it possible to **explain the options chosen for which the interpretations will take into account potential biases**.

Note:

In most cases, a randomised controlled trial can be performed. **However, in some very specific situations, this type of study is not applicable and the use of another experimental plan should be justified**. A guide presenting the methodological choices for clinical development of MDs has been made available by HAS to guide the persons conducting the project. The "Methodological Choices for the Clinical Development of Medical Devices" guide is available on the HAS website (www.has-sante.fr).

► Primary objective

The primary objective must obligatorily be defined before the study protocol is drawn up. It must be unique. Its wording provides elements essential to the indication that the MD will ultimately have on the market.

The difficulty is choosing the right objective for the clinical demonstration of the new MD. In fact, the entire trial is built around the **wording of this primary objective**, which must be clear, precise and based on relevant and valid clinical criteria.

The following elements are specified in the wording of the objective:

- the treatment tested;
- the control treatment, which ideally corresponds to the reference strategy;
- the type of trial: superiority, equivalence, non-inferiority;
- the patients concerned.

For example, "to demonstrate that the aortic endoprosthesis reduces perioperative mortality compared with open surgery in patients suffering from an unruptured aortic aneurysm more than 5 cm in diameter".

The primary objective of a study may be the demonstration of improvement in the patient's quality of life if the product studied has demonstrated its efficacy.

► Primary endpoint

Identification **of a single primary endpoint** is suggested in accordance with the primary objective of the study. **It must be defined before the protocol is drawn up** (see Guide to Methodological Choices for the Clinical Development of Medical Devices) (24) and allow quantification of the therapeutic effect of the new MD in relation to the control treatment.

The choice of primary endpoint must be consistent with the condition treated and the clinical action of the new MD and the control treatment. To obtain a valid demonstration of the clinical benefit of the new MD, the endpoint must be relevant and validated.

It should be at best a clinical criterion or a criterion of convenience of use with clinical benefit for patients.

Endpoints of studies supporting applications for inclusion on the LPPR must also be suitable for the type of technology considered **and be consistent with the claims of the manufacturer.**

Main characteristics of endpoints that can be used in trials:

- short-, medium- or long-term reduction in mortality;
- reduction or improvement in morbidity: pain, scarring, decreased relapses, reduced pain, etc.);

- compensation for disability (degree of dependence and autonomy, recovery of lifestyle, mobility, socio-professional integration, etc.);
- reduction in complications or adverse events from the surgical technique or procedure: number of hospitalisations, duration of hospitalisation, infections, haemorrhages, repeat procedures, etc.;
- improvement in the patient's quality of life;
- impact on the organisation of care: reduction in duration of hospitalisation, decrease in consumption of healthcare products or decrease in number of procedures, decreased use of medical transport, etc.

The aspect of quality of life of patients or people with disabilities is essential.

Quality of life can be a very relevant endpoint for some technologies, in particular those that involve patient adherence for use of the product. This type of criterion must be taken into account as often as possible in studies supporting applications.

The principles concerning primary endpoints are detailed in the document "Assessment principles established by the Medical Device and Health Technology Evaluation Committee (CNEDiMTS) to determine the reimbursement eligibility of medical devices for individual use" (14).

► Eligibility criteria: inclusion and non-inclusion criteria

Ideally, the study population must correspond to the patients for whom this new MD is intended in **current practice**. The eligibility criteria are based not only on a precise description of **clinical forms of the condition** but also on the **characteristics of the patients** to be included: age, sex and comorbidities.

The patients included in the trial must be sufficiently homogeneous so as not to increase variability, which could have too great an effect on the result of the trial. Studies already carried out should assist in the description of the inclusion and non-inclusion criteria of the trial.

The eligibility criteria must correspond to the same indications as the reference strategy and the patients likely to participate in the trial must be able to be included in all of the treatment groups to be compared.

It is important to anticipate the feasibility of the study considering the size of the target population and the calculated sample size necessary to demonstrate the clinical benefit; the clinical forms of the condition must be sufficiently common to allow recruitment of patients within a realistic time frame.

► Choice of comparator

The comparator is derived from the reference strategy according to the current scientific data. It is defined for **a given indication and may or may not be reimbursed.**
The nature of this comparator can vary greatly:

- a product (medical device or medicinal product or another health product);
- and/or a procedure or a group of procedures;
- and/or a service.

The reference strategy is based on reliable **data from the literature**. In the absence of valid scientific evidence, the reference strategy is defined as that used in routine practice according to expert opinion. This reference strategy should be that which, in the absence of the new MD, is supposed to give the **best results** in patients affected by the illness or disability in question.

The last important point involves specifying the **role of the comparator in the therapeutic strategy or compensation for disability**. This specification has the merit of reinforcing the benefit of correctly conducting this trial to ensure demonstration of the potential clinical benefit of the new MD in the care of patients with the condition in question.

The choice to conduct a superiority, equivalence or non-inferiority trial takes into consideration both the existence of a reference strategy and the supposed contribution of the new MD in terms of efficacy compared with the reference strategy.

► Choice of investigator sites

Trials are preferably **multicentre**. The objective is dual; to facilitate:

- patient recruitment to ensure the shortest possible inclusion period;

- extrapolation of the study results. In fact, the different teams participating in the trial will be more representative of a certain variability in medical practice.

The teams likely to participate in a multicentre trial must master the implantation technique or the surgical procedure. When drawing up the study protocol, actual **specifications** are proposed for the **eligibility** of teams that can participate in the trial. The specifications include standardisation of the implantation technique, the experience of the medical team, the required technical facilities and the quality control of medical data.

In the case of practice of procedures and prescription of certain MDs which require a specific framework for public health reasons or which are likely to involve unjustified expenditures, rules established by decree by the Minister of Health, after receiving the opinion of HAS, may be applied. These rules concern in particular the **training** and **qualification** of professionals and the technical conditions for implementation. The use of these MDs and the practice of these procedures may be limited **to certain healthcare organisations for a given period**[36]**.**

► Calculation of the number of subjects required

The *a priori* estimate of the number of patients to be included is essential. The population sample size depends on two variables:

- the expected significance of the therapeutic effect;
- the prevalence of the event being researched.

The greater the therapeutic effect, the fewer patients are needed to demonstrate that a difference is great. On the other hand, if rare events are being researched, the size will be large.

Depending on specific characteristics of the MD, patient recruitment may sometimes be limited. In this case, it may be beneficial to implement **international multicentre studies** and emphasise the support role of assessment agencies.

► Management of protocol deviations and missing data

A bias in the follow-up may appear during the course of the study. This can translate into a difference in the level of study “drop-outs”, namely with treatment discontinuations, patients lost to follow-up or use of concomitant treatments.

Study “drop-outs” can be related to adverse events or a lack of therapeutic efficacy. This may result in a disappearance of the effect related to the treatment, or conversely, the appearance of a false difference.

The experimental plan must be designed to **minimise the number of patients lost to follow-up or who withdraw from treatment**. The manufacturer, in cooperation with the investigators, should implement all possible means to limit these biases.

► Data quality

The protocol must report the methods that will be used to limit the number of patients lost to follow-up and missing data. Quality control of data is essential. It should be described with precision for both the investigator sites and the database used.

► Clinical development strategy

It is essential to have a **strategic and anticipatory vision** from the design of the clinical development plan. This means anticipating, from the outset, the aspects that will add value to the MD until it is made available to the patient.

This approach enables the person conducting the project to **save time** by avoiding, for example, having to start a new trial, in addition to the trial conducted for CE marking at the time of the MD arrival on the market, in order to meet HAS requirements on clinical benefit data from a therapeutic strategy or disability compensation point of view.

If, for example, reimbursement of the MD is planned in France, it would then be appropriate, before implementing clinical research to obtain CE marking, to take into account the clinical requirements that will

[36] Article L.1151-1 of the Public Health Code

be required by the CNEDiMTS in order to anticipate them. **The studies obtained could then be useful throughout the MD pathway.**

4. Post-marketing surveillance and clinical follow-up

Once CE marking has been obtained, surveillance and materiovigilance must be put in place in order to continuously assess the risks associated with the use of the MD. At the same time, once access to reimbursement is obtained, a post-inclusion study may be requested in some cases in order to obtain new data about the **clinical performance** with a view to renewal of inclusion.

4.1 Surveillance and materiovigilance

► Materiovigilance

Materiovigilance concerns all medical devices after their marketing, whether or not they have CE marking, apart from those subject to clinical research[37].

Materiovigilance aims to avoid serious incidents and risks of serious incidents jeopardising medical devices (re)occurring, by taking appropriate preventive and/or corrective measures (25).

Regulation 2017/745 modifies the rules of materiovigilance[37].

► Case-by-case materiovigilance

Manufacturers must report the following to ANSM via Eudamed:

- any serious incident (except those involved in trend reports);
- any corrective safety measure taken with regard to a device on the market in the European Union;
- the report will be made upon establishment of imputability and, in any event, within the time frames specified below:

Table 3. Maximum time frame for materiovigilance before reporting to ANSM

	Serious incident	Death or unanticipated serious deterioration in a person's state of health	Serious public health threat
Maximum time frame for reporting after learning of the incident or threat	15 days	10 days	2 days

Except in an emergency, corrective measures must be reported to ANSM before they are implemented.

Serious incident:

Any incident that directly or indirectly led, might have led or might lead to any of the following:

- the death of a patient, user or any other person;
- the temporary or permanent serious deterioration of a patient's, user's or any other person's state of health;
- a serious public health threat.

Serious public health threat:

An event which could result in imminent risk of death, serious deterioration in a person's state of health, or serious illness that may require prompt corrective measures, and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

These definitions are from European Regulation 2017/745.

[37] Chapter VII of European Regulation 2017/745

Other types of incidents lead to optional reporting to ANSM[38], but should be the subject of a trend report in accordance with Article 88 of Regulation 2017/745.

► Assessment by ANSM

Assessment of incidents by ANSM is carried out in 3 stages. After recording and sorting upon receipt of incident reports, the assessment is organised according to 4 procedures, 3 of which are defined by the criticality (the fourth procedure, independent of criticality, concerns global assessments).

Incidents can be considered **minor**, **major** or **critical**. The methods and the procedure time frames given by ANSM will depend on this classification. A **global assessment** may also be implemented for known incidents of a high frequency; they are then collected and statistically analysed.

Materiovigilance contact person:

The Public Health Code, via Article R.5212-13, specifies that all manufacturers of medical devices, or their representatives, must designate a materiovigilance contact person and report their name to ANSM.

► Periodic summary report and trend report

When similar serious incidents relate to the same device or type of device, the cause of which has been determined or for which a corrective safety measure has been applied, or when incidents are common and well documented, the manufacturer may periodically send summary reports instead of individual serious incident reports[39].

Manufacturers must report, in a trend report via Eudamed, any statistically significant increase in frequency or severity of incidents that are not serious or which are expected undesirable side effects that may affect the risk/benefit ratio and may pose risks to the health and safety of patients[40].

► Post-marketing surveillance

► By manufacturers

For each device, manufacturers design, establish, document, apply, maintain and update a **post-marketing surveillance system** based on the risk class and type of device[41]. This system is an integral part of the quality management system implemented by the manufacturer[42].

This surveillance system enables the active and systematic collection, recording and analysis of relevant data on the quality, performance and safety of a device throughout its lifetime, in order to draw necessary conclusions and to define and apply any preventive or corrective measures and to monitor them.[42]

Documents relating to the post-marketing surveillance make up Annex III of Regulation 2017/745; it is necessary to obtain CE marking. It includes, in particular:

- The **post-marketing surveillance plan** on which the surveillance system is based and which aims to specify the methods and procedures that will be followed to proactively collect and assess clinical data.
  - This surveillance plan must include as a minimum a certain number of elements, including the plan for collection of clinical data to confirm the risk/benefit ratio of the PMCF (previously mentioned in this guide).
- The **periodic safety update report (PSUR)** (classes IIa, IIb, III) and the **surveillance report** (class I) which summarise the results and conclusions of the analysis of the surveillance data, stating the justification for any preventive or corrective measures taken and describing them
  - Post-marketing surveillance report: the report is updated when necessary and made available to the competent authority upon request.

[38] Article R.5212-15 of the PHC
[39] Articles 86 and 87 of European Regulation 2017/745
[40] Article 88 of European Regulation 2017/745
[41] Articles 83 to 86 of European Regulation 2017/745
[42] Article 83 of European Regulation 2017/745

- Periodic safety update report (PSUR): established for each device and where relevant for each category or group of devices:
    - IIa: must be updated when necessary and at least every two years;
    - IIb and III: must be updated annually.

  For class III devices, manufacturers submit the PSUR to the NB involved in the assessment. For other devices, the PSUR is made available to the NB involved.

Changes made by the regulation:

The main changes concern the application for a PSUR or a surveillance report, which are included before development, in the surveillance plan.

► By ANSM

ANSM monitors the marketing conditions of MDs and ensures compliance with the regulations of devices declared by the manufacturer (26). It organises, on its own initiative or when requested by the Ministry of Health, implementation of permanent actions, one-time surveys and thematic programmes.

These market monitoring and assessment operations are not intended to determine the performance of devices, which is the responsibility of the manufacturer, but to demonstrate a possible nonconformity compared to the performance reported and/or compared to the state of the art.

They may correspond to:

- one-time assessments of a single device;
- assessments focusing on an entire category of devices marketed in France.

For each of these assessments, two types of procedures can be used:

- dossier analysis (technical documentation, bibliography, etc.);
- technical analysis performed at the ANSM laboratories or at expert laboratories.

These operations may lead to requests for compliance, recommendations or restrictions of use, or withdrawal from the market.

These operations may also lead to the conclusion that there is no objection to the marketing. This conclusion of the conformity verification must not be presented as an endorsement or a validation of the medical device for commercial or promotional purposes.

Moreover, ANSM performs surveillance of devices with specific risk and innovative devices. This activity is based on data sent by the manufacturers of the sector, and on an innovation watch.

At the national level, ANSM also monitors:

- advertising: verification of compliance of advertising with the regulations in effect;
- respect of technical specifications

4.2 Post-inclusion studies

Requests for post-inclusion studies may occur when a device is included on the LPPR or during certain reviews of generic descriptions and are stated in the opinion of the CNEDiMTS (27). In general, these requests for supplemental studies are the subject of a contractual clause between the CEPS and the company. Post-inclusion studies for medical devices are part of a specific context:

- the short life cycles of MDs with frequent incremental modifications can bring into question the validity of results already obtained with prior versions;
- the assessment of an MD is generally an assessment of the device/operator “pair” and the creation of a protocol must therefore take into account the learning curve of the operators, the experience of the team, the technical facilities, etc.

Post-inclusion studies on MDs aim to answer, for the French people, certain questions that still persist about these products, with a view to their renewal of inclusion or an anticipated re-assessment. These questions are generally of two types:

- the efficacy and safety of use of the device in the target population are not clearly demonstrated: in fact, it is not rare for additional clinical data to be necessary to confirm the efficacy and safety of use of the device in question;
- the transferability of the results of clinical trials to current practice is not ensured: these problems of transferability may occur due to multiple factors (interactions with patient environment, different methods of use compared to those followed in the trials, heterogeneous experience of teams, suboptimal adherence, target population different from that included in the trials, etc.).

Thus, the main objectives of post-inclusion studies on medical devices are to:

- describe the characteristics of user physicians and patients in whom the device in question is used (beneficiary population), the conditions of use of the device (indications, initial clinical and paraclinical assessment and assessment carried out during follow-up, etc.), thus allowing verification of compliance with the indications and recommendations (scope of reimbursement in particular);
- measure the benefits of the device for patients in terms of morbidity and mortality and quality of life, complications, or even the role of the medical device in the therapeutic strategy and its impact on the organisation of care and medico-economic aspects;
- confirm the efficacy and safety of use of the device in the target population. In this case, the study request clearly explains the need to implement a clinical trial. These post-inclusion studies must be differentiated from studies on use included in a post-marketing surveillance process which might be requested by the notified bodies that deliver the CE marking certificate.

The Framework Agreement of 16 December 2011 between the CEPS and the professional organisations concerned[26] specifies the implementation of these studies based on the method of reimbursement of the product or service (generic description, brand name). This Framework Agreement is null and void, but it still serves as a guide in relations between the CEPS and companies or their professional organisations.

The objective of the studies, the obligation to establish a scientific committee, as well as the time frames in which the studies must be conducted and their results obtained are defined in the LPPR inclusion agreement of the product.

Whether or not the study request is at the initiative of the CNEDiMTS, the study protocol must be submitted to the CNEDiMTS so it can give its opinion, within three months, on the ability of the study to answer the questions posed.

The results of conventional studies, including interim results when the agreement so provides, are submitted to the CEPS and to the CNEDiMTS during the application for renewal of inclusion of the MD in question. On the other hand, if they are of a nature that may alter the conclusions of the Committee, these results must be communicated without delay.

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Note:

For any additional questions, a CNEDiMTS FAQ is available on the HAS website (www.has-sante.fr).

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