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A STUDY ON REGULATORY APPROVAL PROCESS OF ACTIVEIMPLANTABLE MEDICAL DEVICES (AIMDs) IN EUROPEAN UNION & REGULATIONS EU MDR 2017/745

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ABSTRACT

The European Medical Device Regulation (MDR) is a set of regulations that governs the production and distribution of medical devices in Europe, and compliance with the regulation is mandatory for medical device companies that want to sell their products in the European marketplace. Manufacturers must develop a suite of MDR-compliant regulatory systems, processes, and documents to continually monitor the safety and performance of their products. The current Medical Devices Regulation (EU 2017/745) has replaced the Medical Devices Directive (93/42/EEC) as the legislation detailing the requirements that manufacturers must meet to place medical devices on the market in the European Union. All manufacturers of Class I to III medical products must familiarize themselves with the new requirements. As one of the highest risk categories of device, Active Implantable Medical Devices (AIMDs) are subject to rigorous regulatory controls before they can reach global markets. The Medical Device Regulation (MDR) (EU) 2017/745 defines the requirements of these medical devices.

KEYWORDS: European Medical Device Regulation, Active Implantable Medical Devices (AIMDs), Medical Devices Regulation (EU 2017/745).

1. INTRODUCTION

Medical Device

As per *Article 2* of EU MDR 2017/745, medical device is defined as[1]

Any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes.

- diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,
- investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,
- providing information by means of *in vitro* examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.

The following products shall also be deemed to be medical devices.

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

MDR Classification Rules as per Annex VIII

The classification of Medical Devices as per EU MDR has been carried out as per *Article 51*and *Annex VIII*basedon **the intended purpose of the devices and their inherent risks.**

1. **Class I** – Provided non-sterile or do not have a measuring function **(low risk)**

Examples: Corrective glasses and frames, Manual wheelchairs

Class 1s Low Risk (Sterile)

Examples: Personal protection kits, Sterile Urine Bags, etc.

Class 1m Low Risk (Measuring Body attributes)

Examples: Stethoscopes, Weighing Balance.

Class 1r Low Risk (Reused Device)

Examples: Surgical forceps, instruments for dental examination, surgical instruments such as scissors, tweezers, lancets.

2. Class IIa (medium risk)

Examples: Orthodontic wires, Surgical gloves, Lancets.

3. Class IIb (medium/high risk)

Examples: Orthopedic nails and plates, Intra-ocular lens, Incubators for babies.

4. Class III (high risk)

Examples: Pacemakers, Prosthetic heart valves, Cardiovascular sutures, Brain spatulas, Drug-Device Combination products

Rules for Classification

The MDR will contain 22 rules for classification – four more than the previous Medical Device Directive (MDD). All the rules are based on the potential risks associated with the device, its technical design, and how the device is manufactured.[1-3]

Rules 1 – 4: Non-invasive devices

Rules 5 – 8: Invasive devices

Rules 9 – 13: Active Devices

Rules 14 – 22: Special rules

2. EU REGULATIONS ON ACTIVE IMPLANTABLE MEDICAL DEVICES (AIMDs) AS PER EU MDR 2017/745

As one of the highest risk categories of device, **Active Implantable Medical Devices** (AIMDs) are subject to rigorous regulatory controls before they can reach global markets. The Medical Device Regulation (MDR) (EU) 2017/745 defines the requirements of these medical devices.[4,5]

Active Implantable Medical Devices (AIMDs)

An Active Implantable Medical Device is defined as.

- A device the operation of which depends on an energy source other than that generated by the human body for that purpose or by gravity, and which acts by changing the density of or converting that energy,

- Which is to be totally introduced into the human body or used to replace an epithelial surface or the surface of the eye by clinical intervention,
- Which is intended to remain in place after the procedure,
- And includes any active device intended to be partially introduced into the human body by clinical intervention and intended to remain in place after the procedure for at least 30 days.

Examples of AIMDs

Source: British Standards Institution (BSI)

Fig-1- Examples of Active Implantable Devices.

All Active Implantable Medical Devices and their accessories **are classified as Class III** and therefore subject to the most rigorous regulatory controls.

AIMDs are subject to rigorous regulatory controls both pre- and post-market. The regulatory controls set out in the MDR also apply to any accessories that are used to enable the device to operate as intended, for example: battery packs, controllers, implant kits, leads, programmers, refill kits, and software applications.[4,5]

Requirements for Active Implantable Devices

As per *Annex I, Chapter II*of EU MDR 2017/745

Active implantable devices shall be designed and manufactured in such a way as to remove or minimize as far as possible.

a) risks which may arise where maintenance and calibration are impossible, including:

i. excessive increase of leakage currents,

ii. ageing of the materials used,

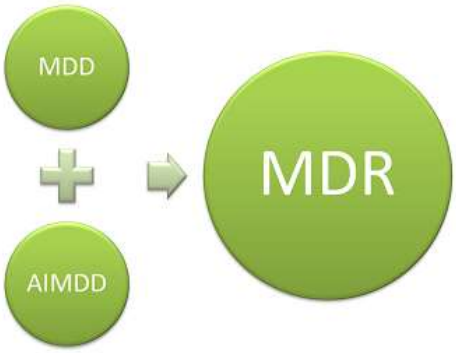
iii. excess heat generated by the device,

iv. decreased accuracy of any measuring or control mechanism.

Active implantable devices shall be designed and manufactured in such a way as to ensure.

a) if applicable, the compatibility of the devices with the substances they are intended to administer, and

b) the reliability of the source of energy.



Implant card and information to be supplied to the patient with an implanted device

As per *Chapter II, Article 18* of EU MDR 2017/745[6]

The manufacturer of an implantable device shall provide together with the device the following.

a) information allowing the identification of the device, including the device name, serial number, lot number, the UDI, the device model, as well as the name, address and the website of the manufacturer;

b) any warnings, precautions or measures to be taken by the patient or a healthcare professional with regard to reciprocal interference with reasonably foreseeable external influences, medical examinations or environmental conditions; any information about the expected lifetime of the device and any necessary follow-up;

Summary of Safety and Clinical Performance

As per *Chapter III, Article 32* of EU MDR 2017/745[7]

The summary of safety and clinical performance shall include at least the following aspects.

a) the identification of the device and the manufacturer, including the Basic UDI-DI and, if already issued, the SRN;

b) the intended purpose of the device and any indications, contraindications and target populations;
c) a description of the device, including a reference to previous generation(s) or variants if such exist, and a description of the differences, as well as, where relevant, a description of any accessories, other devices and products, which are intended to be used in combination with the device;
d) possible diagnostic or therapeutic alternatives;
e) reference to any harmonised standards and CS applied;
f) the summary of clinical evaluation as referred to in Annex XIV, and relevant information on post-market clinical follow-up;
g) suggested profile and training for users;
h) information on any residual risks and any undesirable effects, warnings and precautions

For class III devices and implantable devices, the PMCF evaluation report and, if indicated, the summary of safety and clinical performance referred to in *Article 32* shall be updated at least annually with such data.

Clinical Investigation of Implantable Medical devices

In the case of implantable devices and class III devices, clinical investigations shall be performed, except if.

a) the device has been designed by modifications of a device already marketed by the same manufacturer,
b) the modified device has been demonstrated by the manufacturer to be equivalent to the marketed device, in accordance with Section 3 of Annex XIV and this demonstration has been endorsed by the notified body, and
c) the clinical evaluation of the marketed device is sufficient to demonstrate conformity of the modified device with the relevant safety and performance requirements.

Periodic safety update Reports (PSURs)

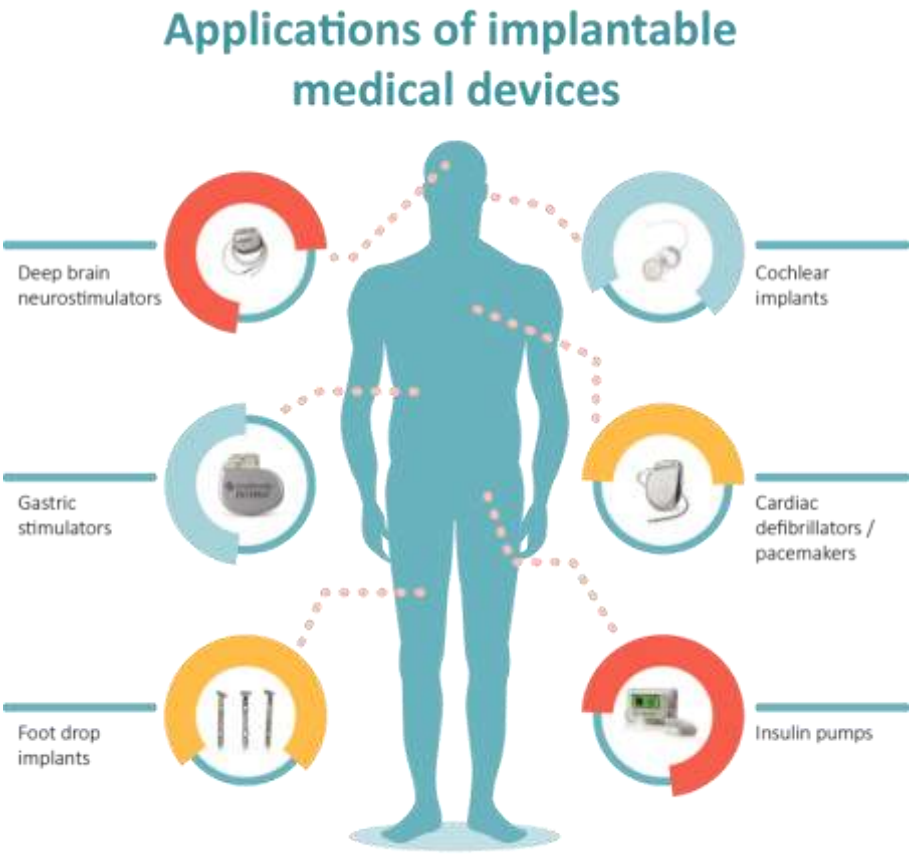
For class III devices or implantable devices, manufacturers shall submit PSURs by means of the electronic system referred to in Article 92 to the notified body involved in the conformity assessment in accordance with Article 52. The notified body shall review the report and add its evaluation to that electronic system with details of any action taken. Such PSURs and the evaluation by the notified body shall be made available to competent authorities through that electronic system.[8]

Other Important Regulations

a) Active implantable devices shall bear a code by which they and their manufacturer can be unequivocally identified (particularly with regard to the type of device and its year of manufacture); it shall be possible to read this code, if necessary, without the need for a surgical operation.

b) For active implantable devices, the serial number, and for other implantable devices, the serial number or the lot number must be in the information of the label Manufacturers shall keep the technical documentation, the EU declaration of conformity and, if applicable, a copy of any relevant certificate, including any amendments and supplements, issued in accordance with Article 56, available for the competent authorities for a period of at least 10 years after the last device covered by the EU declaration of conformity has been placed on the market.

c) In the case of implantable devices, the period shall be at least 15 years after the last device has been placed on the market.[8]



Source: primefeed.in

Figure 2: Active Implantable Medical Devices.

3. EU GUIDELINES FOR APPROVAL PROCESS OF MEDICAL DEVICES FOR MARKETING AUTHORIZATION AND PUTTING INTO SERVICE

The European medical device market represents about 30% of the global market, after the U.S market with a 42% share. The rising geriatric population, an increasing number of surgical procedures (especially orthopedic), and the availability of funding for research and innovation are some of the driving factors for the growth of the medical device market in Europe. A report projects the European medical devices market to reach USD 61.4 billion by 2025 from an estimated USD 48.9 billion in 2020, at a CAGR of 4.7%.[6]

CE marking of conformity

As per *Chapter II*, *Article 20* of EU MDR[9-10]

a) Devices, other than custom-made or investigational devices, considered to be in conformity with the requirements of this Regulation shall bear the CE marking of conformity, as per*Annex V*.

b) The CE marking shall be subject to the general principles set out in *Article 30* of Regulation (EC) No 765/2008.

c) The CE marking shall be affixed visibly, legibly and indelibly to the device or its sterile packaging. Where such affixing is not possible or not warranted on account of the nature of the device, the CE marking shall be affixed to the packaging. The CE marking shall also appear in any instructions for use and on any sales packaging.

d) The CE marking shall be affixed before the device is placed on the market. It may be followed by a pictogram or any other mark indicating a special risk or use.

e) Where applicable, the CE marking shall be followed by the identification number of the notified body responsible for the conformity assessment procedures set out in Article 52. The identification number shall also be indicated in any promotional material which mentions that a device fulfils the requirements for CE marking.

f) Where devices are subject to other Union legislation which also provides for the affixing of the CE marking, the CE marking shall indicate that the devices also fulfil the requirements of that other legislation.

Figure 3: CE Mark.

CE (European Conformity) marking is the medical device manufacturer's claim that a product meets the General Safety and Performance Requirements (GSPR) of all relevant European Medical Device Regulations and is a legal requirement to place a device on the market in the European Union.

Table 1: EU regulatory pathway for CE marking

EU medical device classes	EU regulatory pathway for CE marking [1, 8]
Class I (low risk)	They can be CE-marked by self-declaration of the manufacturer, without the involvement of a Notified Body, once the manufacturer has compiled evidence of conformity with the relevant General Safety & Performance Requirements (GSPR) in EU MDR *Annex I*.
Class I and either: – sterile (Class Is) – with measuring function (Class Im), or -reusable surgical instruments (Class Ir)(low/medium risk)	Their conformity assessment process for CE-marking requires the involvement of a Notified Body only for the specific aspects: sterilization, measuring function, or reprocessing. To that end, the manufacturer must lodge an application with the Notified Body of its choice, and submit the appropriate evidence of Quality Management System and device Technical Documentation.
Class IIa (medium risk)	Their conformity assessment process for CE-marking requires full involvement of a Notified Body. To that end, the manufacturer must lodge an application with the Notified Body of its choice, and submit the appropriate evidence of Quality Management System and device Technical Documentation.
Class IIb (medium/high risk)	Their conformity assessment process for CE-marking requires full involvement of a Notified Body, with higher level of scrutiny than for Class IIa devices, particularly in terms of safety. To that end, the manufacturer must lodge an application with the Notified Body of its choice, and submit the appropriate evidence of Quality Management System and device Technical Documentation.
Class III (high risk)	Their conformity assessment process for CE-marking requires full involvement of a Notified Body. To that end, the manufacturer must lodge an application with the Notified Body of its choice, and submit the appropriate evidence of Quality Management System and device Technical Documentation.

3. THE APPROVAL PROCESS FOR MEDICAL DEVICES IN EUROPE (PREMARKET APPROVAL PROCESS)[11-15]

a) A foreign manufacturer needs to appoint a local representative

b) The sponsor should determine, which category does the device belongs to

c) If the device belongs to class I, non-sterile, and non-measuring, then a QMS is not formally required. However, a PMS procedure is required though not audited by a Notified Body (NB)

d) For those devices that belong to other classes, Quality Management System (QMS) is required, and most companies apply for ISO 13485 standard to achieve QMS compliance

e) The applicant shall prepare a technical file and demonstrate compliance. In the case of the class III device, a dossier must be compiled

f) The QMS and the technical file (dossier in case of class III device) shall be audited by a notified body. For class I, non-sterile, and non-measuring, there is an audit or technical file required

g) Prepare a declaration of conformity[9-10]

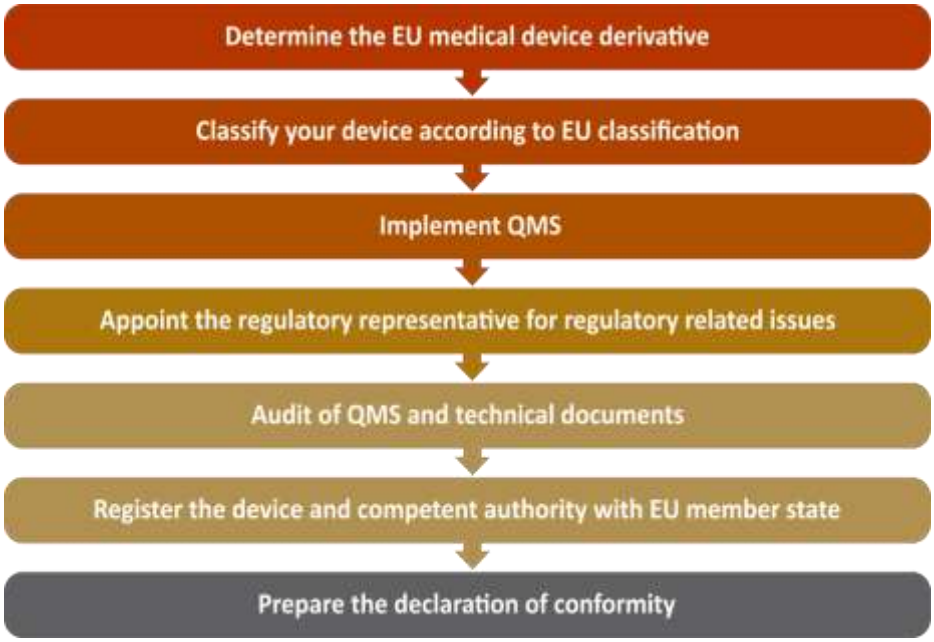


Figure 4: Steps for Medical Devices Market Approval in Europe.

Table 2: Premarket Approval Process in EU.

I (non-sterile, non-measuring)	**I (sterile, measuring)**	**IIa**	**IIb**	**III**
Quality Management System (QMS) not required.	Implement and provide proof of QSM (ISO 13485) compliance.			
Appoint an Authorized Representative (AR) in country that device is to be sold in.				
Submit technical file with necessary documentation and information.				Submit design dossier
No audit required.	Application will be audited by Notified Body (NB).			
N/A	If approved, CE marking will be issued and will be valid for 3 years.			
Prepare and submit Declaration of Conformity (DoC).				
N/A		Some countries within EU require additional registration of Class lla, llb or lll devices.		
If approved, device registration will be granted.				

4. CONCLUSION

The European Medical Device Regulation (MDR) is a set of regulations that governs the production and distribution of medical devices in Europe, and compliance with the regulation is mandatory for medical device companies that want to sell their products in the European marketplace. Manufacturers must develop a suite of MDR-compliant regulatory systems, processes, and documents to continually monitor the safety and performance of their products. The current Medical Devices Regulation (EU 2017/745) has replaced the Medical Devices Directive (93/42/EEC) as the legislation detailing the requirements that manufacturers must meet to place medical devices on the market in the European Union. All manufacturers of Class I to III medical products must familiarize themselves with the new requirements. As one of the highest risk categories of device, Active Implantable Medical Devices (AIMDs) are subject to rigorous regulatory controls before they can reach global markets. The Medical Device Regulation (MDR) (EU) 2017/745 defines the requirements of these medical devices.

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