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CLINICAL EVALUATION AND POST MARKETING SURVEILLANCE OF MEDICAL DEVICES IN EUROPE

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ABSTRACT

In order to market any medical device, marketing authorization from Regulatory authority is required. The process of gaining authorization is multifaceted, multistep and requires review of information by competent authorities. Upon analyzing the information furnished by manufacturer, marketing authorization is granted by the concerned Regulatory authority. In EU, National Authorities give approval for marketing medical devices. A system of third party compliance is followed, where Notified Bodies (Third Party) ensure Quality Assurance, pre and post approval.To obtain a market authorization clinical data such as data regarding the clinical evaluation and clinical investigation of medical devices is needed. Postmarket surveillance is an important safety net and is the practical method to detect medical device problems that occur at too low a frequency orafter prolonged use, or are unlikely to be observed until a product has real-world use**.** The aim of this article is to cover the information regarding the clinical evaluation requirements along with post marketing surveillance system of medical devices in Europe.

INTRODUCTION

Medical Device definition according to EMA

'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes: diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease, — diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability, — investigation, replacement or modification of the anatomy or of a physiological or pathological process or state, providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. The following products shall also be deemed to be medical devices: devices for the control or support of conception; products specifically intended for the cleaning, disinfection or sterilization of devices [1]

Classification of Medical Devices

Devices are divided into classestaking into account the intended purpose of the devices and their inherent risks. It is divided into:

Class I - Low risk

Class II (a) - low/medium risk

ClassII (b) - Medium/high risk

Class III- high risk [1]

Note: All non-invasive devices are classified as class I, All non-invasive devices intended for channeling or storing blood, body liquids, cells or tissues, liquids or gases for the purpose of eventual infusion, administration or introduction into the body are classified as class IIa:

— If they may be connected to a class IIa, class IIb or class III active device; or

— If they are intended for use for channelling or storing blood or other body liquids or for storing organs, parts of organs or body cells and tissues, except for blood bags; blood bags are classified as class IIb. In all other cases, such devices are classified as class I. All non-invasive devices consisting of a substance or a mixture of substances intended to be used in vitro in direct contact with human cells, tissues or organs taken from the human body or used in vitro with human embryos before their implantation or administration into the body are classified as class III.

Market Overview: The medical device market in the EU accounts for one third of the global market, with around $122.5 billion (est. 2011) in yearly revenue. The industry consists of over 22,000 companies all over Europe that employ around half a million people. Many European countries are leaders in medical device innovation and export their products all over the world. Germany, France, and Sweden are very competitive in other markets as well as in Europe. Europe is a major hub for the global medical device industry. However, many European countries export their products to the other markets, and rely on imports to supply the domestic healthcare industry. Manufacturers producing in-demand technologies will find their products are well-received. Recent regulatory, economic, and political shifts in Europe could impact the medical device industry. The medical device manufacturers will transition to the new Medical Device Regulations and ISO 13485:2016, placing significant pressure on Notified Bodies. The relatively weak Euro continues to benefit European companies exporting to the US, but creates difficulties for some importers. Foreign manufacturers will continue to compete with large, multinational corporations operating and distributing in Europe. And, it is important to research the countries where your product will perform best, as healthcare industries vary significantly from one country to the next [2]. Clinical Evaluation of medical devices in Europe Clinical Evaluation of Medical Devices: Clinical investigations of medical devices are of two types:

1. **Pilot clinical investigation**
2. **Pivotal clinical investigation**

Pilot clinical investigation: Used to acquire specific essential information about a device before beginning the pivotal clinical investigation. It is an exploratory study. Involves few number of patients (10-30)

Objectives include:-assessing feasibility, Ascertaining potential harm,Studying device mechanism Validating a method for determining an outcome,Exploring eligibility criteria & their practical application for pivotal controlled investigations. Using a defined device mechanism to validate a surrogate outcome measure & evaluating the logistics of pivotal investigation for performance.

Pivotal clinical investigation: This is a definitive kind of study in which evidence is gathered to support the safety and performance of the medical device for its intended use. It is a confirmatory study Involves large number of patients (150-300)

Post Marketing Surveillance [5]

For each device, manufacturers shall plan, establish, document, implement, maintain and update a post-market surveillance system in a manner that is proportionate to the risk and class and appropriate for the type of device. Data gathered by the manufacturer's post-market surveillance system shall be used to update the technical documentation accordingly. The post- market surveillance system shall be based upon a post-market surveillance plan. Manufacturers of Class I devices shall prepare a post- market surveillance report summarizing the results and conclusions of the data gathered during post- market surveillance. The manufacturer shall prove in a post-marketing surveillance plan that it complies with the essential requirements. The post-marketing surveillance plan shall address the collection and utilization of available information, in particular: Information concerning serious incidents, including information from PSURs, field safety corrective actions; Records referring to non-serious incidents and data on any undesirable side-effect;

Information from trend reporting;

Publicly available information about similar medical devices. Relevant specialist or technical literature databases and/or registers; Reference to procedures to fulfill the manufacturer's obligations. Systematic procedures to identify and initiate appropriate measures including corrective actions. Methods and protocols to communicate effectively with competent authorities, notified bodies, economic users and operators. In general, the period for reporting the adverse events shall be according to the severity of the incident.

Factsheet of Europe

Product – Category	:	Medical device
Market filing	:	EUROPE
Regulating Agency	:	EMA (European Medicines Agency)
Directive	:	EU 2017/745
Classification	:	Class I- low risk Class IIa-low to moderate risk Class IIb-moderate risk Class III-High risk
CLINICAL EVALUATION		
Types of clinical investigation	:	Pilot & Pivotal Investigation
Requirements	:	An application form duly filled in with the required information

Elements required	:	Clinical Investigation Plan Details of the sponsor or the legal representative in accordance with general requirements regarding clinical investigations conducted to demonstrate conformity of devices. Title of the clinical investigation along with the status of the application. Investigator's Brochure Informed Consent A signed statement by the natural or legal representative of the manufacturer of the investigational device that it is in conformity with the general safety and performance requirements. Copy of the opinions of the ethics committee or the other committees concerned. Full details of the available technical documentation [3].
Mode of Submission	:	Electronic submission
Fees	:	Varies in different member state
Timeline for approval	:	Within 30 days
Conduct of the clinical investigation	:	The clinical investigation should be conducted in accordance to the approved clinical investigation plan [4].
Clinical Evaluation Report	:	Within one year of the end of the clinical investigation or within three months of the early termination or temporary halt, a report should be submitted via an electronic system.

Factsheet of Post Marketing Surveillance

Class of devices	**:**	Class II & Class III
Adverse event reporting	**:**	Periodic safety update report (PSUR)
Timeline of Reporting	**:**	Class IIa- at least every two years. Class IIb, III- annually
Mode of submission	:	Electronic submission

Periodic Safety Update Report [6]:

1. Manufacturers of class IIa, class IIb and class III devices shall prepare a periodic safety update report ('PSUR') for each device and where relevant for each category or group of devices summarizing the results and conclusions of the analyses of the post-market surveillance data gathered as a result of the post-market surveillance plan referred to in Throughout the lifetime of the device concerned, that PSUR shall set out:

(a) The conclusions of the benefit-risk determination;

(b) The main findings of the PMCF; and

(c) The volume of sales of the device and an estimate evaluation of the size and other characteristics of the population using the device and, where practicable, the usage frequency of the device. Manufacturers of class IIb and class III devices shall update the PSUR at least annually. Manufacturers of class IIa devices shall update the PSUR when necessary and at least every two years.

Electronic system on vigilance and on post-market surveillance [7]

1. The Commission has, in collaboration with the Member States, set up and

manage an electronic system to collate and process the following information:

(a) The reports by manufacturers on serious incidents and field safety corrective actions

(b) The periodic summary reports by manufacturers

(c) The reports by manufacturers on trends

(d) The PSURs

(e) The field safety notices by manufacturers

(f) The information to be exchanged between the competent authorities of the Member States and between them and the Commission. That electronic system shall include relevant links to the UDI database

Flowchart

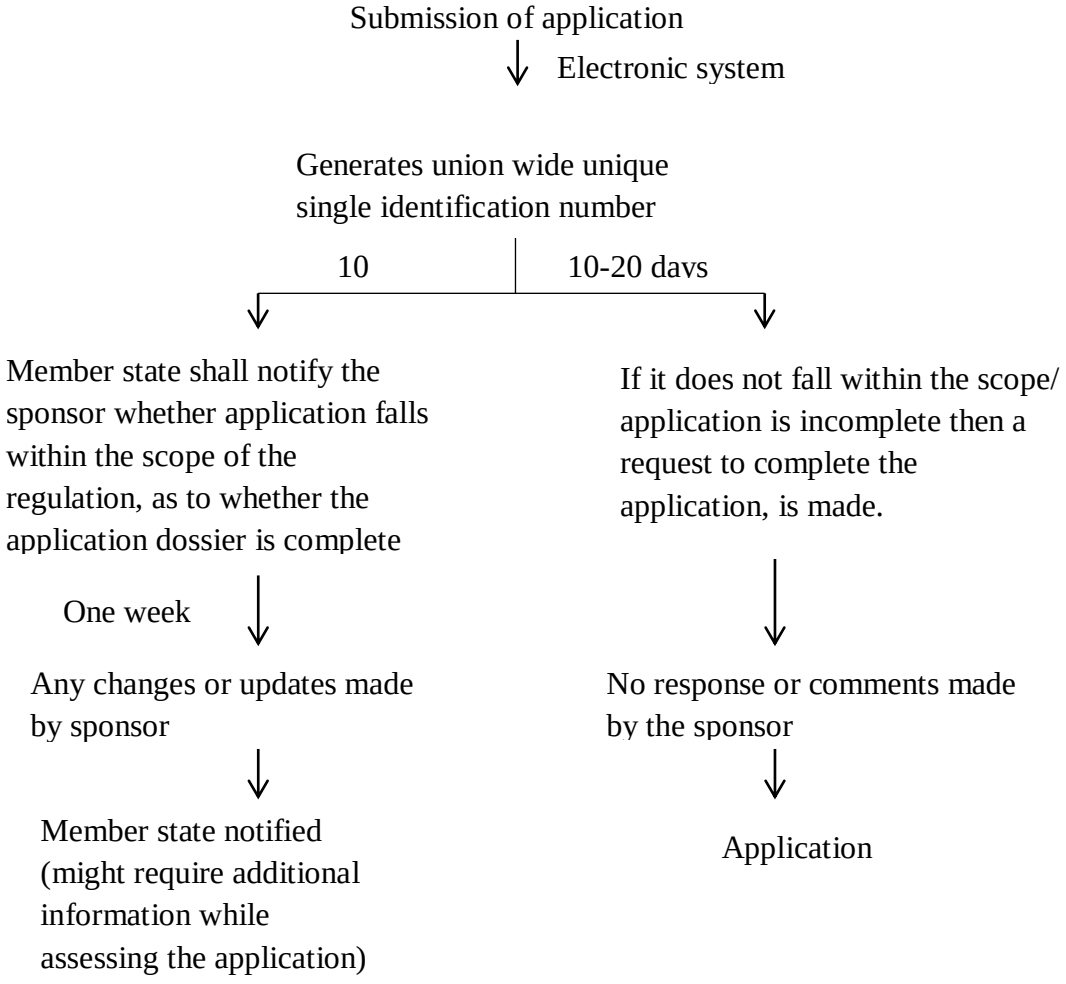

Figure 1: Submission process of application for clinical investigation

CONCLUSION

Every medical device must be supported by a Clinical Evaluation Report (CER) which documents the entire clinical evaluation process. This is mandatory for regulatory compliance and to obtain market authorization for sale of devices in Europe. Due to many issues related to adequate performance of the device the new Medical Device Regulation (MDR) introduced in May 2017 tightened requirements for CERs. For products that are already on the market, companies should be conducting ongoing post-market surveillance to gather data on The real-world use of their devices; this identifies unforeseen risks and complications, as well as areas for improvement. If they have been failing to do this, they will have to begin the time-consuming and costly process of collating data.

REFERENCES

1. Definition and classification of medical devices in europe available at [cited 11 may 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
2. Market overview of medical devices in Europe available at [cited 11 May 2019] https://www.emergobyul.com/resources/market-europe
3. Clinical evaluation of medical devices and its requirements available in Chapter VI, Article 61[cited 12 may 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R074
4. Conduct of clinical evaluation of medical devices available in article 72 [cited 12 may 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
5. Post market surveillance of medical devices in Europe available from Chapter VII, Section I, Article 83 [cited 12 May 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
6. Periodic safety update reports for medical devices in Europe available from Chapter VII, Article 86 [cited at 12 May 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745
7. Electronic system on vigilance and on post-market surveillance of medical devices in europe available from Chapter VII, Article 92 [cited 13 May, 2019] https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017R0745.