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COMPARISION OF MEDICAL DEVICE APPROVAL REGULATIONS IN U.S AND EUROPE COUNTRIES

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ABSTRACT

The knowledge and compliance with regulatory requirements is a key to success in development and marketing of medical devices. As the use of medical devices has increased, stringent regulatory standards are required to ensure safety, efficacy and performance of medical devices with least adverse effects. Recently introduced guidelines help to provide adequate guidance for effective registration by competent authorities, manufacturers and importers. The U.S medical devices regulatory framework is based on FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating and in EUROPE 'The European Medicines Agency (EMEA)' is a decentralized body of the European Union (EU) responsible for medical device regulations. The present article overviews the detailed regulation framework for registration of medical devices in U.S and EUROPE.

Keywords: EMEA, Common Submission Dossier Template, Quality management systems, Filing of medical device license application, Regulation of medical devices.

INTRODUCTION

Medical devices are becoming more important in the health care sector. Medical devices increase the demand for better regulatory frameworks to ensure that products entering the market are safe and efficient. One of the major issues for companies is to be updated on the regulatory requirements and implement them in the process. A company that does not succeed with this may lose thousands of dollars in the delay of marketing the product [1].

GENERAL DEFINITION

The term "Medical Devices" includes everything from highly sophisticated computerized medical equipment down to simple wooden tongue depressors. The intended primary mode of action of a medical device on the human body, in contrast with that of medicinal products, is not metabolic, immunological, or pharmacological [2].

UNITED STATESREGULATIONS

The FDA regulates food, drugs, medical devices, biologics, cosmetics and radiation emitting products in the USA. FDA's Center for Devices and Radiological Health (CDRH) is responsible for regulating manufacturers of 8 medical devices. Medical devices are regulated under the Federal Food Drug & Cosmetic Act (FD&C Act) Part 800-1299.

Classification of medical devices

In the United States medical devices are classified as class I (General Controls), II (Special Controls) or III (Pre-market Approval) devices where class III devices represent the highest risk and require more control. Medical devices are classified through a classification database.

The Medical Device Amendments of 1976 gave the FDA primary authority to regulate medical devices and required the FDA to obtain "reasonable assurance of safety and effectiveness" before marketing. This legislation has been updated several times, including the Medical Device User Fee and Modernization Act of 2002, which established sponsor user fees for application reviews and set performance targets for review times. Each device type

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is assigned by the FDA into one of three regulatory classes on the basis of its risk and the evaluation necessary to demonstrate safety and effectiveness [3, 4].

- Most class I devices (e.g., stethoscopes) are low-risk and subject only to "general controls," such as tests of sterility.
- Class II devices (e.g., computed tomographic scanners) meet general controls as well as "special controls," such as additional labeling requirements. These moderate-risk devices generally pass through the 510(k) review pathway, which refers to the section of the Food, Drug and Cosmetic Act dealing with premarket notification. If a manufacturer can show that its device is "substantially equivalent," additional clinical data are usually not required, although requirements for performance standards and post-marketing surveillance may be imposed.
- Class III products (e.g., deepbrain stimulators and implantable cardioverter–defibrillators) require clinical studies evaluating the safety and effectiveness of the device, called a Premarket Approval (PMA) application [5]. However,class III devices that arise from changes to previously PMA-approved devices may not need additional clinical studies [6,7]. In addition, some older class III devices for which the FDA has not specifically called for PMAs can receive clearance through the 510(k) pathway.

FDA Approval Process for Medical Devices

Step 1:

Identify other similar medical devices to that have already received 510(k) clearance from the FDA, called "Predicate Devices. Visit the FDA Product Classification Search Database page and see the section entitled Medical Devices. Make note of the predicate 510(k) Number, Regulation Number and Classification Product Code.

Step 2:

Using the Product Classification Code; determine whether any Standards and/or Guidance documents apply to the device. These are additional requirements must meet as part of the 510(k) process.

Step 3:

After predicate devices have been identified, must prepare and submit the 510(k) to the FDA. The FDA charges a fee to review the submission.

Step 4:

FDA will review the submission. The FDA reviews most submissions within 90 days and will often follow up with requests for more information. If successful, will receive a 510(k) clearance letter from FDA with 510(k) number.

Step 5:

Go to the FDA Device Registration and Listing page and register the device and company with the FDA. 510(k) number will be required. If located outside the US, must appoint a US Agent at this time as well.

Once forms are submitted online and fees are paid, cleared to sell in the USA! Now becomes subject to inspection for compliance with the FDA Quality System Regulation (21 CFR Part 820) at any time.

THE REGULATORY PROCESS OF MEDICAL DEVICES DEPENDING ON CLASS IN U.S

Class 1 device regulation

- Implement QMS which meets FDA quality system regulation found in the 21 CFR 820
- Full compliance with QSRs. The FDA will not inspect the class 1 or 2 devices manufacturer for compliance prior to device registration but does conduct random inspection and can issue a form 483 for non- compliance
- If have no local representative in the U.S, appoint an FDA US agent representative as local point of contact with FDA.
- List devices and register company using the FURLS system on FDA website in accordance with 21 CFR part 807;contract manufacturer and sterilizers must also register and list
- The FDA listing on their website will serve as authorization to commercialize device in the U.S

Class 2 device regulations

- Implement a QMS which meets FDA quality system regulations(QSR) found in the 21 CFR part 820
- Innovative class 2 devices will likely require clinical studies get pre-submission feedback from the FDA.
- If clinical studies will be required, apply for an investigation device exemption (IDE), develop clinical trail protocol and conduct studies.
- Prepare and submit 510(k) premarket notification application, pay 510(k) review fee to FDA.
- FDA issues 510(k) clearance letter,posts online.
- The FDA will not inspect class 1 or class 2 device manufacturer for compliance prior to device registration but does conduct random inspection and can issue a form 483 for non- compliance.
- Appoint an FDA as agent representative as alocal point of contact with the FDA
- List device and register company using FURLS system on the FDA website in accordance with the 21 CFR part 807
- The FDA listing their website will serve as authorization to commercialization device in the U.S

Class 3 device regulations

- Meets QSRs found in the 21 CFR part 820
- Class 3 will require clinical studies get presubmission feedback from the FDA. If clinical studies required,apply for an investigational device exemption.
- Prepare and submit premarket approval (PMA) application pay PMA submission fee to FDA

- FDA conducts facility inspection of all major supplies involve in the design and production of devices all parties must be with FDA QSR
- FDA issues PMA approval letter,posts online
- Must be in full compliance with the QSRs,the FDA conduct random inspections and can issue a form 483 for non- compliance
- FDA US agent representative as a local point of contact with the FDA
- List device and register company using FURLS system on the FDA website in accordance with the 21 CFR part 807
- The FDA listing on their website will serve as authorization to commercialize device in the U.S this authorization does not expire as long as certain type of changes are not made e.g. design and intended use.

EUROPEAN UNION REGULATIONS

Each country had its own approach to device evaluation [8]. To regulate an uneven and complex market, E.U. directives that outlined requirements under which a medical device (as well as other commercial goods) could be marketed across all E.U. member states after earning a ConformitéEuropéenne (CE) mark in any one member country [9,10]. These directives categorize devices into four classes (I, IIa, IIb, and III) on the basis of increasing risks associated with their intended use [11, 12]. Device approval in each E.U. country is overseen by a governmental body called a Competent Authority, such as the Medicines and Healthcare Products Regulatory Agency in the United Kingdom and the French Agency for the Safety of Health Products. The lowest-risk devices are declared to the Competent Authority, which may conduct inspections to confirm manufacturing standards and review the technical file for the device. Approval for more complex devices is directly handled by Notified Bodies, independent companies that specialize in evaluating many products, including medical devices, for CE marks and are designated by Competent Authorities to cover certain types of devices.

In Europe, registration of medical devices is subject to harmonised European directives established in the 1990s. The core legal framework consists of three directives:

1. Directive 90/385/EEC regarding active implantable medical devices (AIMDD 90/385/EC), Directive 93/42/EEC regarding medical devices (MDD 93/42/EC) and
2. The Directive 98/79/EC regarding in vitro diagnostic medical devices (IVDD 98/79/EC).see table1.

The European Medicines Agency (EMEA) is a decentralized body of the European Union (EU) whose responsibility is to protect human and animal health through the evaluation and supervision of medical products for human or animal use. This information is found at the EMEA homepage. Medical devices are subject to Directive 93/42/EEG and must be CE-marked before entering any country in the EU General order of activities in compliance with European regulations see figure 1. Active implantable medical devices are subject to Directive 90/385/EEG Manufacturers of drugs and medical devices who want to sell their product to a country in the EU only submit one single marketing authorization application to the EMEA.

Classification

Medical devices are divided into class I, class IIa,class IIb and class III where class I also have the subclasses sterile and measuring. The devices shall have a GMDN code. All medical devices exempt class I devices require the involvement of a Notified Body. The classes of medical devices that require involvement of a NB are specified in Table 1. Whether the involvement of a NB is necessary or not.

Medical devices and their accessories are treated as medical devices. Medical devices must meet the essential requirements in Annex I of Directive 93/42/EEG. Standards are used to meet and demonstrate compliance with the essential requirements.

Manufacturers of medical devices must have a qualitysystem. ISO 13485 is normally used. Clinical trials are required for active implantable devices, class III devices and invasive devices for long-term use of class IIa and IIb. Instructions for use are not necessary for class I and IIadevices if they can be used safely without them. A registration of a product is valid for five years [13].

Some examples per class of medical device are provided here (for an exact overview of classification document by the EU):

- **Class I**: urine collection bottles, non-sterile dressings, eye occlusion plasters, stethoscopes, handheld mirrors in dentistry, examination gloves;
- **Class IIa**: tubes for infusion pump, pressure indicator, syringes for infusion pumps, containers or bags for temporary storage and transport of organs, fridges for blood storage, dressings that control the level of moisture of the wound, adhesives fortopical use, stents, tracheal tubes;
- **Class IIb**: hemodialysisers, gradients medium for sperm separation, dressings for chronic extensive ulcerated wounds or severe decubiti's wounds;
- **Class III**: prosthetic or biological heart valves, drug delivery systems, breast implants, hip joint replacements systems.

The Global Harmonization Task Force described further down has developed a recommended classification system where medical devices are divided into class A, B, C and D where class D represents the highest risk. This system is however are commendation to regulatory authorities and not to companies. Information ont he GHTF recommended classification system is found in the GHTF document Principles of Medical Devices Classification.

A nomenclature is usually given to a medical device when it is classified. There are two international nomenclatures that are very common:

- The Emergency Care Research Institute (ECRI) nomenclature called the Universal Medical Device Nomenclature System (UMDNS). The UMDNS terms are harmonized with the classification system of the USA and exist in ten languages [14].
- The Global Medical Device Nomenclature (GMDN) codes. The GMND code is built according to EN ISO 15225 and is collaboration between the EU, EFTA, USA and Canada [15]. The GMDN terms only exist in English but can be translated with special software. This nomenclature system is required for registering a medical device within the EU [16].

Both systems consist of defined terms that describe a group of products with similar characteristics. The GMDN system is developed from 6 different nomenclature systems and the UMDNS system is one of them. GMDN and UMDNS harmonize with each other but GMDN has more terms and is therefore preferred [17].

REGULATORY PROCESS OF MEDICAL DEVICE APPROVALS DEPENDING ONCLASS IN EU

General IVD device classification regulations

- Prepare a technical file (design dossier for list A IVD) which provides detailed information demonstrating compliance with 98/79/EC.
- Appoint authorized representative (EC REP) located in Europe and qualified to handle regulatory issues place EC REP name and address on instruction for use or outer packing or device label whenever sold in the Europe.
- IVDs must be registered with the European competent authority (ministry of health) where authorized representative is based additional notification to other countries may be required.
- Prepare a declaration of conformity a legally binding document prepared by manufacturer starting that IVDs is in compliance with the applicable directive, may now the CE marking to IVD.
- The self-certificate CE-marking certificate does not expire as long as remain in compliance with 98/79/EC.

Self-testing IVDs, list B IVD and list A IVDs device classification regulations

- Implement QMS in accordance with the annex 4/annex 7 of 98/79/EC most companies apply the ISO 13485 standard to achieve QMS compliance
- Prepare a technical file
- Appoints an authorized representative located in Europe and qualified to handle regulatory issues
- QMS and technical file must be audited by a European notified body and third party accredited by the European authorities to audit medical device companies and products. CE marking certificate of device will be issued upon successful completion of the notified body audit
- IVD must be registered with the European competent authority
- Prepare a declaration of conformity
- Audited by a notified body every 6-12 months to ensure ongoing compliance with the applicable annex 98/79/EC. Failure to pass the audit will invalidate CE marking certificate.
- Conduct ongoing batch testing on list - A IVDs classification devices and forward results to notified body.

CE certification procedure

The European market approval system consists of national authorities for separate certification and registration of medical products and is called a decentralized approval system. The decentralized procedure relies on the designated NB that regulates CE marking.

Europe (CE) Approval Process for Medical Devices

In order to commercialize medical and IVD devices in the European Union, a CE Mark certificate is needed. This certification verifies that a device meets all regulatory requirements of the Medical Devices Directive (MDD), In Vitro Diagnostic Device Directive (IVDD) or Active Implantable Medical Device Directive (AIMD) as they apply to the product.

Step 1:

Determine which EU Medical Device Directive applies to the device: 93/42/EEC – Medical Devices Directive (MDD) or 90/385/EEC - Active Implantable Medical Devices Directive (AIMDD):

Step 2:

Determine classification of the device using Annex IX of the Medical Devices Directive (MDD): Class I (non-sterile, non-measuring), Class I (sterile, measuring), Class IIa, Class IIb or Class III/AIMD. Active implantable medical devices are subject to the same regulatory requirements as Class III devices.

Step 3:

Implement Quality Management System (QMS) in accordance with Annex II or V of the MDD, for all devices except Class I (non-sterile, non-measuring). Most companies apply the ISO 13485 standard to achieve QMS compliance.

Step 4:

Prepare a Design Dossier for Class III/AIMD devices. Prepare a CE Technical File for all other devices that provides detailed information on medical device demonstrating compliance with MDD 93/42/EEC.

Step 5:

Appoint an Authorized Representative (EC Rep) located in Europe. They should be qualified to handle regulatory issues. Place EC REP name and address on Instructions for Use and, packaging.

Step 6:

For all devices except Class I (non-sterile, non-measuring),QMS and Technical File or Design Dossier must be audited by a Notified Body, a third party accredited by European authorities to audit medical device companies and products.

Step 7:

For all devices except Class I (non-sterile, non-measuring), will be issued a European CE Marking Certificate for the device and an ISO 13485 certificate for facility following successful completion of Notified Body audit. CE Marking certificates are typically valid for 3 years. ISO 13485 certification must be renewed every year.

Step 8:

All Class I devices must be registered with the Competent Authority where EC REP is based. Most EU member states do not require registration of Class IIa, IIb or III devices.

Step 9:

Prepare a Declaration of Conformity, a legally binding document prepared by the manufacturer stating that the device is in compliance with the applicable Directive. Now affix the CE Marking.

Once a medical device has undergone an assessment and complies with the requirements of the applicable regulation, a CE marking (Figure 2) shall be affixed to the product according to Article 18 of the 'Proposed Regulation'. The CE marking indicates that a product qualifies to be freely distributed within the market of the European Economic Area (EEA), however it does not indicate that the origin of the product is in the EEA.

CE certification

The designated NBs of specific EU member state and countries having a regulatory agreement with the EU are registered in the EU New Approach Notified and Designated Organizations' (Nando) information system. Dependent on the national regulation for the specific MD category and class (to be found on the website of the national medicine authority; in The Netherlands this is the Inspectie voor de Gezondheidszorg (IGZ) supported by the CBG-MEB), these NBs can be approached for a decentralised approval procedure. The appointed NB for the healthcare and medical products in The Netherlands is DEKRA Certification B.V.

The standards for a CE certificate vary per NB, but obtaining CE marking may require relatively little data:

- for devices that are substantially equivalent to an existing product, a comparative literature review may be sufficient;
- for certain low-risk class medical devices (Class I, no Is or Im), companies can certify the device themselves without the involvement of a NB.
- higher-risk devices almost always require human validation data, but (other than medicine trials) trials need not be randomised and often address safety but not efficacy.

The procedure comprises the following actions:

- initial agreement on the regulatory strategy towards product classification and Primary Mode of Action (PMoA) claims; if a medical device contains a pharmacological, immunological or metabolic mode of action, then it has to be assessed by the CBG-MEB (Medicines Evaluation Board);
- agreement on the category and class definition of a medical device (highest risk part is leading);in case a manufacturer is in doubt whether a product is classified as MD class I orhigher, a NB must be consulted since registration within NOTIS does not verify if aproduct is correctly classified as a class I MD;
- compliance with QMS requirements;
- build-up of a technical file.

Conformity assessment

The MDD 93/42/EC defines products into different classes, based on risk and intended use, which determine the relevant conformity assessment procedure. For products classified with medium to high degree of risk (class Is, Im, IIa, IIb and III) the MDD requires a conformity assessment procedure involving a notified body or not (Table 1). The stringency of the conformity assessment procedures depends on the class of the medical device. For each class, the manufacturer has the choice between two or more conformity assessment procedures (see Table 2). Each of the conformity assessment procedures consists of the application of one or more Annexes out of Annexes II to VII of the MDD. The clinical evaluation must be part of the documents which the manufacturer submits to the NB for assessment.

Annex II section 4 applies only to class III MDs and this section is similar to Annex III with the difference that in-house test results obtained by the manufacturer under full quality management system may be used as the basis of certification.

The manufacturer may thus choose the ISO 13485 standard in combination with the respective guidance standard as the basis of the QMS or use an equivalent quality system suitable to fulfill the requirements of the MDD.

Additionally in Annex VIII, MDs are described that are excluded from CE certification.

These comprise:

- MDs intended for clinical investigations (the requirements here include METc approval, device description, researcher and patient identification, IGZ notification);
- Custom-made MDs;
- Home-made/home-use MDs.

TECHNICAL FILE

The purpose of a CE technical dossier is to show compliance with the essential requirements for one single product (family). In general it must be emphasized that a

technical file is seen as a controlled document that will need to be updated where relevant. It is the responsibility of the legal manufacturer to obtain the technical file and keep it updated, but the actual production activity may be outsourced; a copy present at the manufacturing site is very useful. The technical file is commonly based on a STED layout.

A Summary technical Document (STED) is a harmonised format for submitting information for regulatory approval of new medical devices. The STED format was created by the Global Harmonization Task Force (GHTF) with the long-term goal to globally standardize regulatory submissions. The five GHTF members (Australia, the EU, Japan, Canada and the United States) have evaluated STED as a pilot program likely reducing inter-country differences in technical dossiers. A revised format of the STED layout for medical devices is expected in due time. The core components of a technical file based on STED layout are:

General aspects of the device

These aspects include the manufacturer, critical subcontractors, manufacturing site certifications and worldwide regulatory status of the product type.

Device description

This description should include extended descriptions of all components and accessories of the device, their functional characteristics, technical performance specifications (e.g. accuracy, sensitivity, specificity, and reliability) andother specifications (e.g. chemical, physical, electrical, mechanical, biological, sterility, stability, storage).

Essential principles and evidence of conformity

List of standards per part of the system, Essential requirements

Risk management

This includes a risk management plan for the lifetime of the product, risk analysis for the various components, the manufacturing process and the clinical use during the various phases of the lifetime of theproduct. For risk management, several techniques can be used, e.g. Fault Tree Analysis(FTA; IEC 61025) and Failure Modes and Effects Analysis (FMEA; IEC60812) during the design, FMEA during production, Post Market Surveillance/Compliant/ CAPA when the product is on the market. Risk analysis is preferably performed following the ISO 14971:2012 standard.

Summary of design verification/validation

Design assurance, safety of medical electrical devices, electromagnetic compatibility, software validation protocol, sterilization, packaging,shelf-life, biological safety, biocompatibility and clinical evidence.

Manufacturing information

Description of manufacturing process for product and accessories indicating quality control (QC) operations

Labeling

All labels, product brochure, instruction for use, technical manual and maintenance.

DECLARATION OF CONFORMITY

The manufacturer must draw up the Declaration of Conformity (DoC) to declare his sole responsibility for the conformity to the relevant Directive. The DoC is a proof of compliance with EC regulations to the involved to the authorities and customs and must be delivered with each product sold or with each batch of identical products sold to the same end user.

In contrast to medicinal products, medical devices do not require any pre-market authorization by a regulatory authority. Instead a conformity assessment is performed with the objective to demonstrate compliance with the 'General safety and performance requirements'. The respective medical device class, i. e. the identified risk related to a medical device, determines the level of control associated with the conformity assessment procedure.

Article 42 of the 'Proposed Regulation' outlines the various conformity assessment procedures to be executed before putting the device on the market. They range from a declaration issued by the manufacturer himself without involving a third party to a conformity assessment based on full quality assurance and design dossier examination, involving a notified body. The technical documentation and the Declaration of Conformity according to Article 17 of the 'Proposed Regulation' are considered as key documents to prove compliance with the legal requirements for medical devices, because these two items are part of each of the above mentioned routes of conformity assessment, with a varying level of detail. Once the notified body has confirmed the product's compliance, the manufacturer issues the Declaration of Conformity, confirming that compliance with the 'General Safety and Performance Requirements' of the 'Proposed Regulation' has been demonstrated. See Annexure 1 of this work presents a template of the EC Declaration of Conformity.

COMPARISION OF REGULATORY APPROVALS OF MEDICAL DEVICES IN U.S AND EUROPE

The table 3 comparison the authority, classification of devices relating to their risk, process of registration depending on class, submission process in approvals, data requirements in approval process depending on class, time of approvals, expiring of device registration ,difficulties to face risk in regulatory approvals depending on class either simple or complexity and overall cost of regulatory approvals depending on class risk from low to high cost approvals.

1

Table 1. Overview of medical devices directives, categories, classes and lists

EU Directive	Device category	Class/list	NB involvement	Dutch registration	European registration
MDD 93/42/EC	Medical device	class I	X	NOTIS system (CIBG/Farmatec)	Eudamed
		class I_s	√ to assess "sterile" or "measure" aspect	IGZ via NB	
		class I_m			
		class IIa	√	IGZ via NB	
		class IIb			
		class III			
IVDD 98/79/EC	High-risk IVD	list A	√	IGZ via NB	
		list B			
		self-tests			
	Low-risk IVD	other	X	NOTIS system (CIBG/Farmatec)	
AIMDD 90/385/EC	AIMD	n/a	√	IGZ via NB	

Table 2. The conformity assessment procedures depend on the class ofthe medical device

Conformity assessment procedure	Medical device class					
Annex	**I**	**I_s Sterile**	**I_m Measure**	**IIa**	**IIb**	**III**
II (+ section 4)						√
II (- section 4)		√	√	√	√	
III					√	√
IV		√	√	√	√	√
V		√	√	√	√	√
VI		√	√	√	√	
VII	√	√	√	√		

Table 3. Comparison of medical device approvals in U.S and Europe

U.S	EUROPE
Authority	
US FDA's (CDRH)	EMEA
Classification of devices simple in U.S, complex in E.U	

Approval Process registration

Applicable medical device regulations/ directives

Code of Federal Regulations (CFR), Title 21, Parts 862–892	• **Medical Device Directive 93/42/EEC** regulates most devices. Classification rules are listed in Annex IX of the directive. • **Active Implantable Medical Devices (AIMDs) Directive 90/385/EEC**. AIMDs are regulated as high-risk devices. • ***In Vitro* Diagnostics (IVDs) Directive 98/79/EC**. Most IVDs are regulated as low-risk devices, except for tests that underpin the safety of blood and blood products (blood group, HIV and hepatitis tests), where additional specific requirements equating to a high-risk category apply. • **Subsequent directives:** A number of additional directives amending the original directives have been introduced: • Directive 2007/47/EC amends Directive 90/385/EEC and Directive 93/42/EEC • Directive 2001/104/EC brings medical devices incorporating stable blood derivatives within the scope of the general directive • Directive 2003/12/EC reclassifies breast implants into class III • Directive 2003/32/EC relates to medical devices that are manufactured utilizing tissues of animal origin Directive 2005/50/EC reclassifies total hip, knee and shoulder joints into class III

Steps in submission process of approvals

1.based on FDA classification database involves * type of device *name of device **2.based on FDA 510(k) process involves** ***predicate 510(k) number *FDA regulation number *classification product code **3.determain special guidance documents or international standards such as** *electrical safety *software validation **4.prepare and send the 510(k) submission to the FDA** **5. FDA will review submission within 90 days**	**1.define directive** **2.verify requirements** **3.involvement of notified body depend on class** *MD class$1_{s/m,}$class 2 and class3 *IVD list A/B *AIMD *find NB via nando **4.check conformity in** *QMS *declaration of conformity **5.submission of technical documents and STED layout** **6.CE marketing**

Data requirements for registration depending on class

-For class 1 and class 2 devices ***pre-market notification data and *510(k) application are required **-For class 3** *pre-market approval application	**For low-risk MD** *for class 1 and class 2a devices -declaration of conformity with essential requirements -details of conformity assessment procedures ***for class3 MDs and high risk devices** -technical documentation and STED layout document -EC certificates issued by notified body

Time of approvals in EU

IVD classification in Europe	How long you should expect to wait after submission until approval is granted. (See note 1)	Validity period for CE Marking certificate. (See note 2)	Registration renewal should be started this far in advance. (See note 3)	Complexity of the registration process for this classification. (See note 4)	Overall cost of gaining regulatory approval. (See note 5)
General IVD Self-certified	<1 month	Does not expire	Not applicable	Simple – Complex	Low – High
Self-Testing IVD*	3-5 months	3 years	2 months	Simple – Complex	Low – High
List B IVD (Annex II)	3-5 months	3 years	2 months	Simple – Complex	Low – High
List A IVD (Annex II)	9-12 months	3 years	2 months	Simple – Complex	Low – High

TIME OF APPROVALS IN US

Device classification in USA	How long you should expect to wait after submission until approval is granted. (See note 1)	Validity period for device registrations. (See note 2)	Registration renewal should be started this far in advance. (See note 3)	Complexity of the registration process for this classification. (See note 4)	Overall cost of gaining regulatory approval. (See note 5)
CLASS I*	1 month	Does not expire	Not applicable	Simple – Complex	Low – High
CLASS II	3-6 months	Does not expire	Not applicable	Simple – Complex	Low – High
CLASS III**	18-30 months	Does not expire	Not applicable	Simple – Complex	Low – High

Annex 1. Template EC declaration of conformity issued and signed by the manufacturer

DECLARATION OF CONFORMITY

MANUFACTURER: *NAME AND ADDRESS*

EUROPEAN REPRESENTATIVE: *NAME AND ADDRESS*

PRODUCT: *NAME, TYPE AND/OR MODEL*

CLASSIFICATION: *CLASS, RULE ACCORDING TO ANNEX IX OF THE MDD* (NOT MANDATORY BUT RECOMMENDABLE)

CONFORMITY ASSESSMENT ROUTE: *ANNEX APPLIED*

WE HEREWITH DECLARE THAT THE ABOVE MENTIONED PRODUCTS MEET THE PROVISIONS OF THE COUNCIL DIRECTIVE 93/42/EEC FOR MEDICAL DEVICES. ALL SUPPORTING DOCUMENTATION IS RETAINED UNDER THE PREMISES OF THE MANUFACTURER.

STANDARDS APPLIED: *LIST OF (HARMONIZED) STANDARDS FOR WHICH DOCUMENTED EVIDENCE OF COMPLIANCE CAN BE PROVIDED*

NOTIFIED BODY: *NAME, ADDRESS AND IDENTIFICATION NUMBER*

(EC) CERTIFICATE(S): *EC CERTIFICATE(S) NUMBER(S)*

START OF CE-MARKING: *DATE, LOT NUMBER OR SERIAL NUMBER OF FIRST CE-MARKING*

PLACE, DATE OF ISSUE: *CITY, DATE*

SIGNATURE: _____

NAME
POSITION

Fig 1. General order of activities in compliance with European regulations

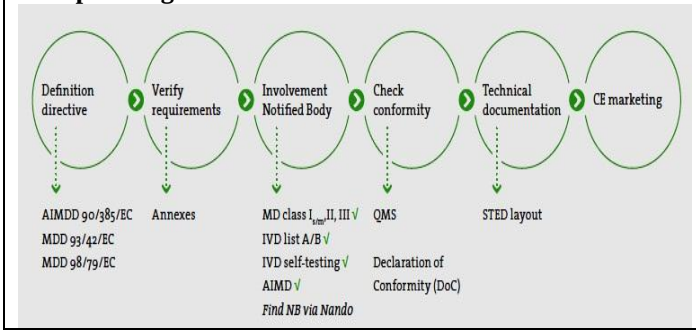
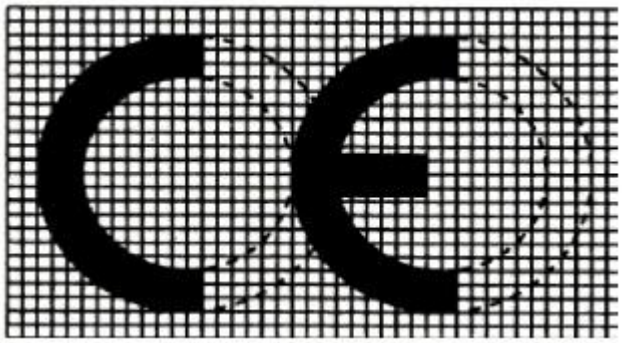


Fig 2. CE marking



CONCLUSION

Both Systems for approving new medical devices must provide pathways to market for important innovations while also ensuring that patients are adequately protected. To achieve these goals, the United States and European Union use a combination of premarket testing and post-market vigilance but with some marked contrasts in their approaches. Features of both environments require reform, as well as continuing research to assess policy changes. Europe is known worldwide as a leader in medical device innovation the best and most advanced life-enhancing and life-saving devices in the world are developed in Europe. It is widely acknowledged that European manufacturers are heavily challenged during commercialization of new medical devices and that the moment of market introduction is crucial in this highly competitive market. At the same time, safety, risk reduction and conformity to regulations are not to be moved past. Still, Europeans have access to the latest medical devices on average 3-5 years sooner than people in other parts of the world. This difference is owed to the relatively large number of medical device innovators and the decentralized approval system that efficiently reviews the safety and performance of new medical devices without causing unnecessary delay. Research has also shown that Europe's system is just as safe as the centralized system used in other parts of the world such as the US. This renders Europe currently the most attractive market for introduction of medical devices. However, because of recent changes in EU regulations on MDs and IVDs it is unsure for how long still. In addition, it should be kept in mind that introduction of European devices towards the USA is anexhaustive procedure.

REFERENCES

1. Anand K. To Recognize the Use of International Standards for Making Harmonized Regulation of Medical Devices in Asia-Pacific. *Journal of Young Pharmacist*, 2010, 241.
2. World Health Organization, Definition of medical device, http://www.who.int/medical_devices/en.
3. Maisel WH. Medical device regulation: an introduction for the practicing physician. *Ann Intern Med*, 140, 2004, 296-302.
4. Medical devices: device classification. Silver Spring, Food and Drug Administration, April 27, 2009 (http://www.fdagov/ Medical Devices/ Device Regulation and Guidance/ Overview/ Classify Your Device/default.htm)
5. Sapirstein W, Alpert S, Callahan TJ. The role of clinical trialsin the Food and Drug Administration approval process for cardiovasculardevices. *Circulation*, 89, 1994, 1900-2.
6. FDA should take steps to ensure that high-risk device typesare approved through the most stringent premarket review process. Washington, Government Accountability Office, 2009.
7. 21 Code of Federal Regulations, 814, 2011.
8. Chai JY. Medical device regulation in the United States and the European Union: a comparative study. *Food Drug Law J* , 55, 2000, 57-80.
9. Fraser AG, Daubert JC, Van de Werf F, *et al*. Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform. *Eur Heart J*, 32, 2011, 1673-75
10. European Council. Directive 93/42/EEC concerning medical devices, 1993.
11. European Commission. Classification of medical device, 2010.
12. http://www.lne-gmed.com/pdf/en/ annex9-directive-93-42-amended.pdf.
13. European Commission, Directive 93/42/EEC, 2014.
14. ECRI Institute, Universal Medical Device Nomenclature System http://www.ecri.org/Products/Pages/UMDNS.aspx, printed 10/04/2008.
15. http://www.mercosur.int/msweb/portal%20intermediario/es/index.htm,printed17/12/2007.
16. Medical Products Agency, Global Medical Device Nomenclature, 2006.
17. U.S Food and Drug Administration, Brockton Hefflin and Larry Kessler, The Global Medical Device Nomenclature, http://www.ncvhs.hhs.gov/030819.