National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

Comparison of market authorization systems of medical devices in USA and Europe

RIVM Letter report 2015-0001
A. van Drongelen | J. Hessels | R. Geertsma

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Colophon

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Medische hulpmiddelen variëren van relatief eenvoudige producten als pleisters en rolstoelen tot complexe apparatuur, zoals pacemakers en MRI-scanners. Op verzoek van de Inspectie voor de Gezondheidszorg (IGZ) heeft het RIVM de markttoelatingssystemen voor medische hulpmiddelen in de Verenigde Staten en Europa met elkaar vergeleken. Wanneer de eisen die beide systemen stellen naast elkaar worden gelegd, kan niet geconcludeerd worden dat het ene systeem tot veiligere medische hulpmiddelen leidt dan het andere.

Het uitgangspunt van beide toelatingssystemen is dat medische hulpmiddelen worden ingedeeld in risicoklassen. Naarmate het risico groter wordt, neemt de zwaarte van de toelatingsprocedure toe. Een belangrijk verschil is dat het markttoelatingsproces in de Verenigde Staten volledig wordt uitgevoerd door de overheid (Food and Drug Administration). In Europa wordt dit uitgevoerd door bedrijven die hier specifiek voor zijn aangewezen (*notified bodies*), en onder toezicht van de nationale overheden staan. Ook verschilt de manier waarop de risicoklasse wordt bepaald. In Europa bestaan daarvoor vast omschreven eisen, in de Verenigde Staten is dat diffuser.

Op beide systemen is kritiek ontstaan over de manier waarop de veiligheid en werkzaamheid van medische hulpmiddelen op de markt worden gegarandeerd. De kritiek richt zich vooral op producten die op de markt zijn toegelaten doordat zij gebruikmaken van gegevens over de veiligheid en werkzaamheid van andere, al toegestane producten. Fabrikanten claimen dan dat hun eigen product gelijkwaardig is aan deze bestaande producten. De veiligheid en werkzaamheid van de nieuwe producten hoeven daardoor met aanzienlijk minder eigen onderzoeksgegevens te worden aangetoond. Dit is zowel in de Verenigde Staten als in Europa mogelijk. Recente voorbeelden hiervan, die via beide systemen tot de markt zijn toegelaten, en waarmee onverwachte problemen zijn opgetreden, zijn metaal-op-metaal heupimplantaten en bekkenbodemmatjes. In reactie op dit soort problemen zijn verbeteringen in de systemen voorgesteld, die gedeeltelijk zijn ingevoerd. Als voorbeeld hiervan zijn in Europa de eisen die aan de notified bodies worden gesteld aangescherpt en wordt het toezicht geïntensiveerd.

Trefwoorden: medische hulpmiddelen, wetgeving, markttoelating, FDA, Europa

Abstract

Medical devices are a group of products varying from relatively simple devices like plasters and wheelchairs to complex equipment like pacemakers and MRI scanners. At the request of the Dutch Health Care Inspectorate, the RIVM has compared the market authorization systems for medical devices in the United States of America (USA) and Europe. Based on the comparison of the requirements of both systems, it cannot be concluded that one or the other system leads to safer medical devices on the market.

The basis of both authorization systems is the categorisation of medical devices in different classes. Devices in higher risk classes are subject to more stringent conformity assessment procedures to obtain market authorization. An important difference between the two systems is that the market authorization procedures in the USA are performed entirely by the government (Food and Drug Administration), while in Europe these are performed by companies (Notified Bodies) designated and supervised by the government. Another difference is that Europe has a strict set of rules to categorise the devices in their risk classes, while the USA follows a much more diffuse approach.

In both Europe and the USA, the systems have been criticized with regard to guaranteeing safety and effectiveness of medical devices on the market. An important focus of the criticism has been on products obtaining market authorization by using safety and effectiveness data of existing products on the market. The manufacturers claim equivalence between their product and the existing product. This way, they need to generate significantly less data on their own product to substantiate safety and effectiveness. This is possible in the USA as well as in Europe. Recent examples of products that were allowed on the market through both systems using equivalence, and that have led to unexpected adverse effects, are metal-on-metal hip implants and transvaginal meshes. In response to this type of problems, improvements for both systems are being proposed, which are partially implemented. As an example in Europe, requirements for Notified Bodies have been made more stringent and their supervision has been intensified.

Keywords: medical devices, legislation, market authorization, FDA, Europe

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Summary

RIVM conducted a basic comparison of the market authorization procedures of medical devices for Europe and the USA to provide a general understanding of the similarities and differences of both market authorization systems. To perform this comparison, the current legislation in both the USA and Europe were compared for several aspects like marketing authorization procedures, governmental involvement and technical requirements. This study was performed at the request of the Dutch Health Care Inspectorate.

In both systems, medical devices are classified into several risk classes. For higher risk classes, the effort required to gain market authorization increases. Equivalence to existing devices on the market can be used to allow easier market authorization. For products in the lowest risk class, the manufacturer is the only responsible party for market access. Therefore, the basic concept of both systems is comparable.
Building on the similar basic concept, a number of differences are introduced by the two systems. In the USA, granting market authorization for higher risk devices is done by the government (Food and Drug Administration, FDA), whereas companies, designated and supervised by the national authorities, are responsible in Europe. For the risk classification of the devices, detailed classification rules are available in Europe, whereas there are no detailed rules in the USA, where the classification is done by the FDA. In the USA, reclassification of a device is an easier process than in Europe. In the USA, the market authorization procedure for high risk devices does not allow equivalence to be used for easier market authorization and the manufacturer is always required to perform one or more clinical studies, which can take one or more years. In Europe, also for the high risk devices, equivalence can be used as part of the market authorization procedures. This difference explains why certain devices can take several years longer to come onto the USA market, compared to Europe. The procedure for high risk devices is only used for 1% of the devices in the USA.
In the USA, no requirements for substantially equivalent devices are elaborated, except for substantiation of equivalence. For high risk devices it is specified that non-clinical laboratory studies and clinical studies involving human subjects need to be included. In Europe, general, "essential requirements" related to safety, performance, design and construction are listed, to which the manufacturer has to demonstrate compliance, as far as applicable, for a specific medical device. Harmonized European standards can be used to show compliance to several essential requirements, and standards contain a checklist linking clauses of a standard to specific essential requirements. In the USA, standards can also be used in the process of market authorization. However, the FDA determines which standards can be used and can exclude parts of a standard.
Information on the performance of a medical device after it has been released to the market (so-called post-market surveillance, PMS), can provide important information to the manufacturer and the authorities. In both systems, manufacturers are required to report the occurrence of severe incidents with their medical devices to the authorities and explain how they will act upon it. Moreover, in Europe, every manufacturer is required to have a systematic procedure to review experience gained from devices in the post-production phase, which is intended to be more than a complaint handling system. In the USA, the FDA can order PMS studies to be performed for certain devices.
In the USA, most information related to the market authorization of medical devices is publicly available at the FDA website. In Europe, information on

market authorization is collected in a database, which is only accessible to Competent Authorities. The information in this database is not yet always up-to-date or complete.

The strict requirements for high risk devices in the USA prevented some devices, which were shown to lead to problems during clinical studies, to come onto the USA market, whereas they were allowed on the European market. On the other hand, requiring long clinical investigations to be performed can delay the availability of critical medical devices to patients. This highlights the balance between safety and availability of medical devices that a legislative system should provide.

Several highly publicized problems with medical devices, e.g. metal-on-metal hip replacements and transvaginal meshes, which were available on the market both in the USA and in Europe, indicate that both systems were not perfect. In Europe, the need to make changes to the medical device legislation was felt for some time, but recent highly publicized incidents intensified the discussion. Several measures were taken on a short notice to reach a higher and more uniform level of competence of Notified Bodies. Moreover, a proposal for new legislation for the market authorization of medical devices was published in 2012 and is now being debated by member states as well as the European Parliament. Also in the USA, changes to improve the market authorization of medical devices have been advocated.

In conclusion, it cannot be stated, based on the requirements, that one system will lead to a different level of quality and safety than the other when correctly applied.

1 Introduction

1.1 General

It is often argued that new medical devices are marketed several years earlier in Europe than in the United States of America (USA), as the legislation in the USA is stated to be stricter than in Europe. To be able to assess and respond to this sort of statements, the Dutch Health Care Inspectorate (IGZ) requested RIVM to conduct a basic comparison of the market authorization procedures for Europe and the USA. In Europe, the regulatory framework for the market authorization of medical devices consists of three main directives (90/385/EEC, Active implantable medical devices [1], 93/42/EEC, medical devices [2], 98/79/EC, in-vitro diagnostic medical devices [3]). These directives are supplemented by a number of amending or implementing Directives, Commission Regulations and several other legal reference documents. For the purpose of the comparison in this document, we will use only the Medical Devices Directive (MDD), since this covers most of the devices. The USA counterpart is the Medical Device Amendments of May 28, 1976, to the Federal Food Drug and Cosmetic Act (FD&C Act) [4] and the Food and Drug Administration Modernization Act of 1997 (FDAMA) [5]. In this last act, the regulation of food, drugs, devices and biological products by the FDA is specified, also covering regulation for market authorization of medical devices.

1.2 Scope

This study is intended to provide a general understanding of the similarities and differences of the market authorization systems for medical devices in the USA and Europe. This study is not intended to provide a detailed comparison of both systems.

2 Methodology

2.1 Collecting information on market authorization systems

The website of the FDA was used as the main source to collect information on the market authorization system in the USA. Additional information was searched by using the internet search engine Google.
For the European system, the text of the current European directives was used, together with the information provided on the website of the European Commission on the medical devices legislation.
Articles discussing one or both of the regulatory systems were searched by checking the last two years of the magazine Clinica, evaluating the European proposal for a medical devices regulation and using the internet search engine Google.

2.2 Comparing the regulatory systems

In order to compare both regulatory systems at a general level, the following main themes were selected:

- Marketing authorization procedures
- Governmental involvement
- Technical requirements
- Mutual recognition
- Decision making
- Post-marketing requirements
- Transparency

Provisions in both systems were described for each theme, and discussed using the authors' knowledge of regulatory systems and information from Clinica and selected internet sources.

3 Marketing authorization procedures

3.1 Classification of medical devices

In both the USA and Europe, classification systems are used as a basis for the market authorization procedures. The classification of medical devices makes a distinction between low, medium and high risk devices. The classification of the device determines the (choice of) approval procedure that has to be followed to obtain market authorization.
The intention of the risk classification of medical devices is to apply an accurate level of control required to assure safety and effectiveness of the device. The most stringent marketing authorization procedures are required for devices, which are considered to present the greatest risk.

3.1.1 USA

In the USA legislation, no explicit rules about the classification could be identified. The following description was found, providing insight into the idea behind the classification in the USA. [6]
Class I
Devices not purported to be for a use, which is of substantial importance in supporting, sustaining or preventing impairment of human life or health, and the devices do not present a potential unreasonable risk of illness or injury.
Class II
Devices for which it is necessary to establish a performance standard, in order to provide reasonable assurance of safety and effectiveness.
Class III
Devices for which insufficient information is available to establish a performance standard. The devices are purported to be for a use which is of substantial importance in supporting, sustaining or preventing impairment of human life or health, or the devices present a potential unreasonable risk of illness or injury.

Device types and specific devices have been assigned by the FDA to one of these three risk classes.
FDA has organized 18 medical specialty panels, in which over 1700 distinct types of devices are described. For each of these types of devices, a general description including intended use, the class to which the device belongs and information about marketing requirements are specified. A manufacturer can search the classification database or go to the applicable device panel and find the type of device there. As an example, a scalpel was entered into the classification database and was determined to belong to device type "878.4800 Manual surgical instrument for general use", which is Class I. [7]
For a completely new device, the risk class cannot be established from these lists and the FDA will have to be contacted to establish the risk class.

In the USA, there are two ways to reclassify a medical device. The first way is applicable for existing devices. The FDA may, on its own initiative or in response to a petition from an interested person, reclassify a device type based on "new information." The new information received about a device must be publicly available "valid scientific evidence".
If the FDA is proposing to reclassify the device from Class II to Class III, the available scientific evidence must show that more stringent measures are required to guarantee the safety and effectiveness of the device. If, on the other hand, the FDA is proposing to reclassify the device to a lower risk class there

must be sufficient valid scientific evidence to guarantee that the safety and effectiveness of that device type can be assured through the less stringent regulatory controls of the lower class.
The procedure to reclassify a product has changed from a rulemaking to an administrative order process in 2012. In 2013 and 2014, seven products were placed from Class III in a lower risk class, whereas only one product was placed in a higher risk class. [8]

The second way for reclassification is intended for novel devices. By definition, a novel device is classified as a Class III device, regardless of the level of risk it poses. For low to medium risk novel devices, for which there is no substantially equivalent device, a *de novo* request can be submitted by the manufacturer. The *de novo* procedure requires FDA to consider the risk of the device and decide on its classification. If a device is classified as Class I or II, it can be marketed immediately and can serve as a predicate device in future. The assessment of the device can be considered to be part of the *de novo* process. [9]

3.1.2 Europe

In Europe, medical devices are assigned to one of four regulatory classes: Class I, IIa, IIb and III. The classification of a device is governed by classification rules, described in Annex IX of the MDD. These rules are based on criteria such as the duration of use, invasive nature, contact with critical parts of the body, biological effect and the supply of energy. To facilitate the use of the classification rules, a guidance document containing explanation and examples was written. If a new medical device is developed, it can be classified by applying the classification rules. This does not require a special decision by a regulatory body. In case of doubt, a Notified Body or a Competent Authority can be asked for advice. [10]

In specific cases, the classification of medical devices as resulting from the classification rules can be changed. Such a decision will be laid down in a directive. Devices which have been reclassified to Class III are breast implants and hip, knee and shoulder joint replacements (directive 2003/12/EC and directive 2005/50/EC). [11] [12]

3.2 Procedures for market authorization

3.2.1 USA

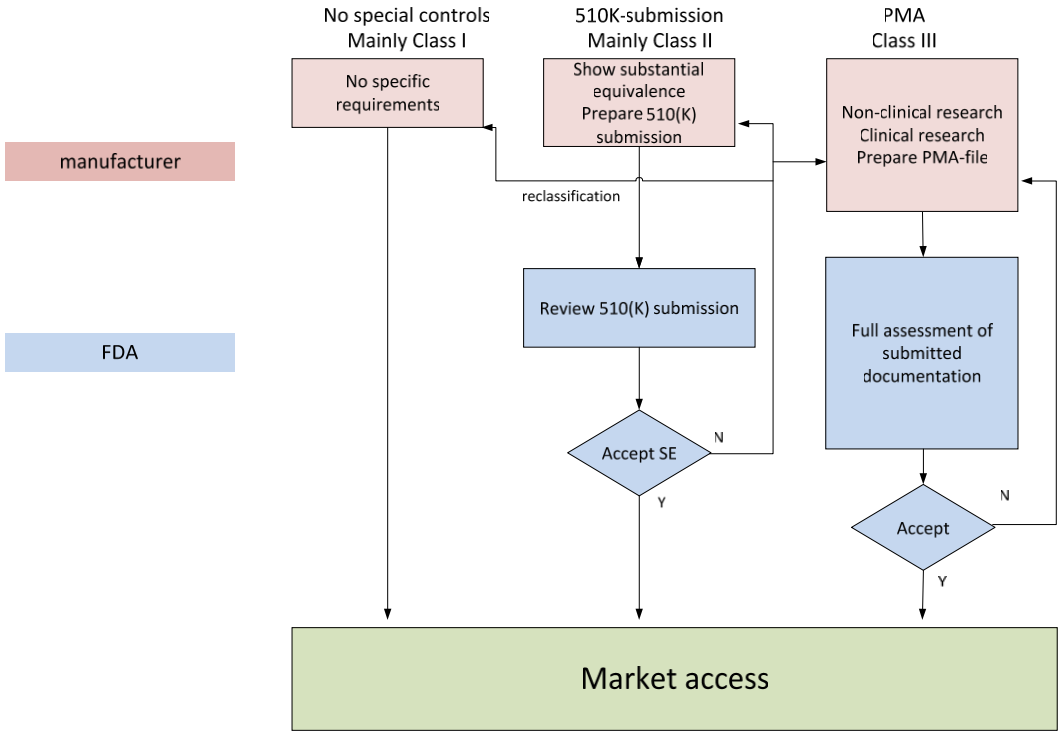
Legislation concerning medical devices is governed by the Medical Device Amendments of May 28, 1976, to the Federal Food Drug and Cosmetic Act (FD&C Act). For general medical devices, this Act is implemented by regulations Title 21 Code of Federal Regulations (21 CFR) Parts 800-1299. The definition of a medical device, classification, conformity assessment and registration requirements are described in these Parts.

Once the classification for the new product is known, the correct market submission procedure can be followed. There are two main procedures for market submission requiring FDA involvement: Pre-market Notification or 510(k) and Pre-market Approval (PMA). In general, the following rules apply:
- Most Class I devices are exempt from 510(k)
- Most Class II devices require 510(k)
- Most Class III devices require PMA

The most stringent form of market submission is the PMA procedure, for which the manufacturer has to submit an extensive set of documents to the FDA. For the 510(k) procedure, the manufacturer has to show that his device is

substantially equivalent to another, already marketed device. It should be noted that the route of substantial equivalence is only valid for eligible devices (mostly Class II) and not for any device for which a substantially equivalent device is available. [13]
A flow chart of the market authorization process is presented in figure 1.

Figure 1: Flow chart market authorization process USA (slightly simplified)



3.2.1.1 Pre-market Approval (PMA)

A PMA is the assessment process of FDA for the safety and effectiveness of most Class III medical devices. Because of the high risks associated with these devices, FDA has determined that special controls (as described for 510(k) approval) alone are not sufficient to guarantee safety and effectiveness of the product. Therefore, a PMA is required for these devices.

The PMA documentation, that has to be submitted by the manufacturer, includes both administrative elements and scientific evidence sections. Although the scientific part is the main part of the document, an application will not be assessed if the document lacks certain administrative elements. If certain clinical data or scientific arguments are lacking, the assessment process will be delayed. It is therefore recommended to manufacturers to have their applications reviewed before submission to FDA.

There are two scientific evidence sections in a PMA application:

- Non-clinical research: This section contains information on, among others, the microbiology, toxicology, immunology, biocompatibility, wear and shelf life of the product. Non-clinical research has to be performed in accordance with certain regulations, defined in 21 CFR Part 58.

- Clinical research: This section has to contain at least study protocols, safety and effectiveness data, adverse reactions and complications, patient information and results.

A Class III medical device with a denied PMA is considered to be adulterated, and is not allowed to be marketed. [14]
This procedure for market authorization is used for about one percent of all devices allowed onto the USA market. [15]

3.2.1.2 Pre-market Notification (510(k))

A 510(k) is a pre-market notification to FDA in which it is shown that the device to be marketed is at least as safe and effective as a similar device which is already legally marketed in the USA. This approach is valid for most Class II devices. This comparison with an existing similar device is called showing substantial equivalence, and the existing device that is used for comparison is called the predicate.

A device is substantially equivalent if in comparison with the predicate:
- it has the same intended use, and the same technological characteristics,

or
- it has the same intended use, and has different technological characteristics, but the information submitted to FDA:
    - Doesn't raise new questions on safety and effectiveness, and
    - Demonstrates that the device is at least as safe and effective as the legally marketed predicate.

For devices for which a 510(k) procedure is applicable, 510(k) must be submitted to FDA when:
1. A device is commercially distributed for the first time, and was not marketed by the firm before May 28, 1976 (pre-amendment device).
2. A different intended use is proposed for a device which the firm already has in commercial distribution.
3. A change or modification of a legally marketed device is made, which could significantly affect its safety or effectiveness. It is recommended to record the justification for submitting or not submitting a new 510(k) in the change control records.

The mandatory elements of a 510(k) include (amongst others):
1. A sufficiently detailed description of the device, allowing the determination of substantial equivalence.
2. An identification of the predicate device, to which substantial equivalence is claimed.
3. An explanation of the intended use of the device. When these explanations differ from the predicate, an additional explanation must be provided, describing why these differences will not have influence on the safety and effectiveness of the device.
4. If the device has the same technological characteristics as the predicate, a summary must be provided in which the technological characteristics of the new device are compared to the predicate. If the device has different technological characteristics, a summary must be provided in which it is explained in what way the technological characteristics are similar to the predicate's characteristics.

FDA will answer to the 510(k) submission by sending a letter, indicating whether FDA agrees on substantial equivalence. If this is so, the device is declared substantially equivalent (SE), and can be marketed in the USA.

If FDA determines the device is not SE, the device would automatically become a Class III device. The submitter can:
- submit another 510(k) with new data;
- request for a revision of classification to a Class I or II device for which a 510(k) is not required (this is known as the *de novo* procedure, see underneath);
- submit a PMA application.

For Class II devices, regulatory requirements referred to as special controls apply. FDA classifies devices in Class II for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information to establish special controls to provide such assurance.
Special controls are usually device specific and include:
- Performance standards
- Post-market surveillance (PMS)
- Patient registries
- Special labeling requirements
- Pre-market data requirements
- Guidelines

In some cases, Class III devices can obtain market authorisation using the 510(K) procedure. An example is a metal-on-metal hip implant, as these are pre-amendment devices.
Pre-amendment devices only require a PMA if the FDA has published a decision to that effect. [13]

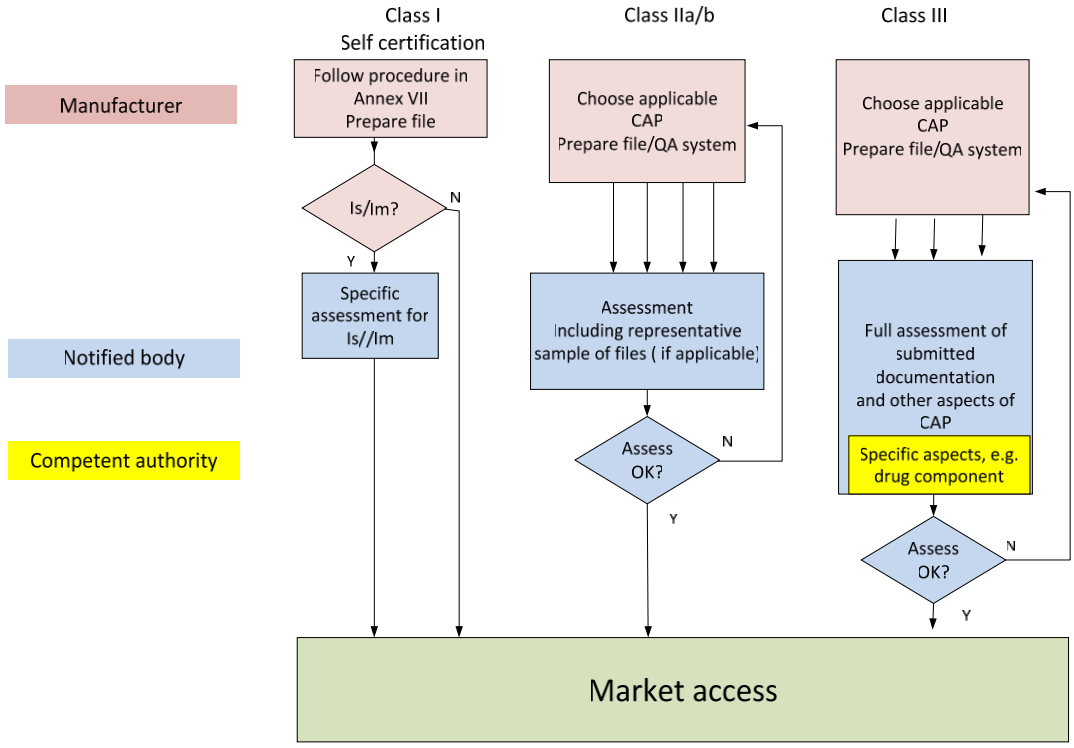
3.2.1.3 Exempt devices

Most Class I devices are exempt from 510(k) notification. Market access therefore does not require the involvement of FDA, apart from device listing and establishment registration (see 4.3.1).

3.2.2 Europe

The conformity assessment procedures that can be used in a marketing authorization procedure are defined in annex II – VII of the MDD. In table 1 below, a description of annexes II - VII is shown. Table 2 provides an overview of which procedure(s) can be used for medical devices from the different classes. A flow chart of the market authorization process is presented in figure 2.

Figure 2: Flow chart market authorization process Europe (slightly simplified)



For Class I medical devices, the conformity assessment procedure is performed without intervention of external parties. However, two specific groups of Class I devices are defined for which there is limited intervention of external parties for the assessment procedure: sterile devices (Class Is) and devices with a measuring function (Im) (annex VII, see table 2).

The parties involved in the conformity assessment procedures (CAPs) for non-Class I devices are Notified Bodies. Notified Bodies are companies that can perform the specific tasks required in the CAPs. The Notified Bodies are designated by and under the supervision of the Competent Authorities in the country where they are based. The national authority will regularly perform audits to check whether the Notified Bodies perform their duties adequately. In 2013, the Commission Implementing Regulation 920/2013 on the designation and the supervision of Notified Bodies in the field of medical devices was published. [16] It contains a number of provisions aimed at reaching a higher and more uniform level of competence of Notified Bodies across Europe, including for example the use of joint assessment teams to audit the Notified Bodies. These teams consist of a representative of the responsible designating authority, two representatives of other member states and a representative of the European Commission. Also in 2013, Commission Recommendation 2013/473/EU on the audits and assessments performed by Notified Bodies in the field of medical devices was issued, specifying how to perform audits and assessments, including for example the principle of "unannounced audits". [17]

The stringency of the involvement of the Notified Bodies increases when the device class rises from IIa, IIb to III. The manufacturer can choose from a number of CAPs depending on the device risk class (see table 1 and 2).

Table 1 Conformity assessment procedures in the MDD

Annex	***Conformity assessment procedure***	***Characteristics***
II	EC Declaration of Conformity (full quality assurance system)	Full quality assurance system for the design, manufacture and final inspection of the device. Subject to audit and surveillance by Notified Body. The extent to which attention is given to individual products depends on the risk class, see notes under table 2
III	EC Type-examination	Notified Body ascertains and certifies that a representative production sample fulfils the essential requirements of the directive.
IV	EC Verification	Manufacturer ensures and declares that the device conforms to the type described in the EC Type-examination certificate and satisfies the essential requirements of the directive. Notified Body examines and tests every device batch (or a statistically representative number) in order to verify conformity of the device with the technical dossier.
V	EC Declaration of Conformity (production quality assurance)	Quality assurance system for the manufacture of the device. Subject to audit and surveillance by Notified Body.
VI	EC Declaration of Conformity (product quality assurance)	Quality assurance system for the final inspection and testing of the device. Subject to audit and surveillance by Notified Body.
VII	EC Declaration of Conformity	Manufacturer ensures and declares that the device satisfies the essential requirements of the directive. Manufacturer affixes the CE marking to each product and draws up a written declaration of conformity as well as a technical dossier. This is the procedure for self-certification.

Table 2 Conformity assessment procedure related to the classification

Device class	***Procedure***
I	Annex VII
Is and Im*	Annex VII + IV **or** Annex VII + V **or** Annex VII + VI
IIa	Annex II** **or** Annex VII + IV **or** Annex VII + V **or** Annex VII + VI
IIb	Annex II*** **or** Annex III + IV **or** Annex III + V **or** Annex III + VI
III	Annex II**** **or** Annex III + IV **or** Annex III + V

* *For Is and Im, the assessment of the Notified Body is limited to aspects of manufacture concerned with either securing and maintaining sterile conditions or the conformity of the product with the metrological requirements.*

** *For at least one representative sample for each device subcategory, assessment of the technical documentation.*

*** *For at least one representative sample for each generic device group, assessment of the technical documentation.*

**** *For each Class III medical device, the Notified Body has to examine the design dossier.*

3.3 Registration of economic operators and devices

3.3.1 USA

For owners or operators of places of business (also called establishments or facilities) it is required to register annually with the FDA if they are involved in the production and distribution of medical devices intended for use in the USA. Most establishments that are required to register with the FDA are also required "to list the devices that are made there and the activities that are performed on those devices". Registration and listing provides FDA with the location of medical device establishments and the devices manufactured at those establishments. Knowing where devices are produced increases the ability to prepare for and respond to public health emergencies. [18]

3.3.2 Europe

In Europe, according to Article 14 of the MDD, manufacturers (or their authorized representatives) of devices belonging to Class I, other than devices which are custom-made or intended for clinical investigations, are required to register with a Competent Authority when placing medical devices on the EU market. The Competent Authority must be in an EU member state where the registered place of business is located. If a manufacturer has no registered place of business in an EU member state, a legal person established in the EU must be designated to act on his behalf, a so-called authorized representative.
In comparison to the USA, this means that only the manufacturers, and no other economic operators involved in the distribution of medical devices, need to register and it is only intended for a limited group of medical devices. The European database EUDAMED should contain more information on manufacturers and medical devices, but this database is not yet fully implemented and therefore has limited value at the moment, although the European Commission published a Commission decision that all required data shall be entered into EUDAMED no later than April 2012. However, in October 2012 an evaluation of EUDAMED was published, indicating that "EUDAMED is not fully able to meet today's expectations about a European databank in terms of completeness, data quality, interlinkage and transparency'. The transposition of the current Medical Devices Directives into national law is heterogeneous;

consequently, the national information systems show heterogeneous data which translates into heterogeneous data in EUDAMED." [19] [20]

3.4 Marking of medical devices

A medical device that is legally placed on the European market should bear a CE mark. If a Notified Body is involved in the market authorization procedure, the identification number of that Notified Body should accompany the CE mark.
There doesn't seem to be an FDA approval mark for medical devices, which would be comparable to the CE mark in Europe. However, there is a certification label applied on electrical appliances: the Federal Communications Commission (FCC) mark. If a device intentionally emits radio waves, the product cannot be sold in the USA without this FCC mark.
Although there is no official mark for FDA-approved devices, all devices cleared or approved by the FDA can be found in publicly available databases. [21] [22]

4 Governmental involvement

4.1 USA

PMA and 510(k) submissions are approved or declined by FDA. This means there is direct involvement of the government.
For the preliminary assessment of 510(k) submissions, non-governmental third party reviewers (so-called Accredited Persons) can be used to expedite the approval process. The Accredited Person conducts the primary review of the 510(k) submission, then forwards its review, recommendation, and the 510(k) submission to FDA. However, the government retains final authority over device approval (see also section 8.1, on decision making). [23]
For combination products (products comprised of two or more regulated components (i.e., drug/device, biologic/device, drug/biologic, or drug/device/biologic), the FDA's Office of Combination Products will assign one of the FDA centers responsible for any of these three types of products as the lead center. This assignment is based on a determination of the "primary mode of action" of the combination product. [24]

4.2 Europe

For the procedures of market authorization for medical devices, there are three levels of governmental involvement:

- No involvement (Class I devices), apart from notification to the national Competent Authority, see section9.2.2;
- Indirect involvement by supervision of the Notified Body that has direct involvement (Class Is/Im, IIa/IIb, and III);
- Direct, but partial, involvement of a Competent Authority. This exception applies for products incorporating a drug substance, products utilizing animal tissue under Directive 722/2012/EC)n some countries additional national measures have been implemented.

In many cases, only a Notified Body is directly involved. A Notified Body is designated by the authorities of the member state in which it is based and is operating under supervision of this Competent Authority. The governmental involvement is limited to supervision of the Notified Body and arbitration in case of dispute. A medicines Competent Authority (medicines evaluation board) is involved directly in case a device incorporates, as an integral part, a drug substance with ancillary action to that device. In that case the authority only has an advisory role for the Notified Body. However, the Notified Body cannot issue a certificate when the advice of the Competent Authority was negative, without consulting the Competent Authority on this matter. The involvement is restricted to the drug substance part of the device, but includes the results of the clinical evaluation to allow the Competent Authority to form an opinion of the benefit-risk ratio of the medical devices incorporating the medicinal product. Therefore, the advice of the Competent Authority can also include issues related to the medical devices.
For devices falling under Commission Regulation 722/2012/EC (regulation for medical devices manufactured utilizing tissues of animal origin), medical devices Competent Authorities are involved; a summary of the assessment by the Notified Body is evaluated by one or more CA's. [25]

5 Technical requirements

5.1 Legislative requirements

5.1.1 USA

For a 510(k) submission, no requirements for the substantially equivalent device are stated, as the requirements for the device are indirectly covered by the device to which equivalence is shown. For 510(k)s, only requirements for demonstrating substantial equivalence are given.
The PMA documentation must include separate sections on non-clinical laboratory studies and on clinical investigations involving human subjects. The specific requirements for particular medical devices are not clearly defined by the FDA. Also, there is no direct connection between fulfilling the requirements in recognized consensus standards and fulfilling the legal requirements.
Only for a small group of devices specific requirements are given, as title 21 Code of Federal Regulations (21 CFR) Parts 1010-1050 describes performance requirements for electronic, ionizing radiation emitting, microwave and radio frequency emitting, light-emitting and sonic, infrasonic and ultrasonic radiation-emitting products. These requirements, which are called standards in the legislation, are mandatory, and mainly cover limits on emission and exposure and describe the mandatory warning labels that should be affixed to these products.

5.1.2 Europe

Annex I of the MDD provides general requirements, covering 8 pages, regarding safety, performance, design and construction of medical devices (so called 'essential requirements').
Although these requirements are worded in general terms only, as they are applicable for all types of medical devices, they provide the framework for identifying all aspects to be addressed. These requirements are mandatory, as far as applicable for the medical device concerned. Following general requirements on safety and performance of the devices during its life time, items specifically mentioned are

- chemical, physical and biological properties
- infection and microbial contamination
- construction and environmental properties
- protection against radiation
- requirements for medical devices connected to or equipped with an energy source
- user information to be supplied with the device

Harmonized standards, see next section, can be used to show compliance to the essential requirements.

5.2 Standards and guidelines

5.2.1 USA

There are several guidance documents provided by FDA. These documents are for the industry and FDA staff, and include a wide range of subjects such as voluntary audit report submission, medical device tracking and review and inspection of PMA applications.
These documents are meant to describe the least burdensome approach in meeting medical device regulation. [26]

FDA has a recognized consensus standards database, in which consensus documents from all standards organizations on a number of categories can be found. The FDA indicates whether they accept the complete standard or whether certain parts are excluded (e.g. standard ISO 10993-10 on tests for irritation and skin sensitization, for which some parts are excluded by FDA). For the use of standards, the FDA's Center for Devices and Radiological Health (CDRH) states "FDA CDRH believes that conformance with recognized consensus standards can support a reasonable assurance of safety and/or effectiveness for many applicable aspects of medical devices. Therefore, information submitted on conformance with such standards should have a direct bearing on safety and effectiveness determinations made during the review of PMAs. In 510(k)s, information on conformance with recognized consensus standards may help establish the substantial equivalence of a new device to a legally marketed predicate device". [27] [28]

5.2.2 *Europe*

For medical devices, there is an extensive package of consensus and interpretative documents.
The official European website for medical devices legislation also refers to official consensus statements (e.g. guidance for Class I manufacturers) and interpretative documents (e.g. on the relation between medical devices and personal protective equipment). [29] The European Association for Notified Bodies for Medical Devices has developed so-called NB-MED recommendations, giving guidance with regard to Notified Body interpretations of a variety of regulatory requirements. [30]

To facilitate uniform interpretation of the requirements in the medical devices legislation, so-called MEDDEV guidelines have been drawn up by representatives of Competent Authorities and Commission Services, Notified Bodies, industry and other interested parties. These guidelines are developed by working groups installed by the European Commission. The MEDDEV guidelines are not legally binding. MEDDEV-guidelines cover topics as classification, Notified Bodies, clinical investigations and evaluation and market surveillance. [31]

For medical devices, harmonized European standards are available, under the supervision of European standards bodies (European Committee for Standardization CEN; European Committee for Electrotechnical Standardization CENELEC). Their references are officially published on the European Commission website. [32] All parties concerned can participate in the drafting process of a standard. Although the standards are voluntary, they serve as a tool to comply with the essential requirements. The standards cover a very broad range of topics, e.g. risk management, clinical investigations, biological evaluation, sterilization, and individual categories or types of devices, e.g. medical gloves, wheelchairs, lung ventilators, and surgical implants. Each harmonized standard, that can be used to show compliance with the essential requirements, contains one or more annexes (so-called Annexes Z) that links clauses in the standard to the essential requirements in the MDD.

5.2.3 *Global guidance*

Besides official standards, the International Medical Device Regulators Forum (IMDRF, follow-up of the Global Harmonisation Task Force (GHTF); a worldwide cooperation between the major medical device regulatory authorities) prepares voluntary guidelines aiming at worldwide harmonization of legislation. Although the European Commission is an active member of IMDRF and these guidelines

are consensus documents, these guidelines have no official status in Europe and are not referred to on the official webpage of the European Commission dealing with the legislation on medical devices. [33]

5.3 Clinical data requirements

5.3.1 USA

Clinical data are required in a PMA application, which means that clinical data are required for most Class III devices (not all Class III devices need PMA, as described in section 4.2). The required clinical data include study protocols, safety and effectiveness data, adverse reactions and complications, device failures and replacements, patient information, patient complaints, tabulations of data from all individual subjects, results of statistical analyses, and any other information obtained from the clinical research.

Clinical studies on human subjects must comply with Good Clinical Practices regulations. These regulations include Protection of Human Subjects, Institutional Review Board (IRB) and Investigation Device Exemption. Guidance on these requirements is available on the FDA/CDRH website. There are three classes of Investigational Device Studies: Significant Risk (SR) Device Studies, Non-Significant Risk Device Studies and Exempt Studies. For an investigational device that is a significant risk device, approval of the study by both FDA and an IRB is required. For an Investigational Device that is a Non-Significant Risk Device, only an IRB approval is required. Exempt Studies (e.g. a comparison study of approved devices, used within their indications for use, without additional risk for patients) do not require approval by an IRB or the FDA. [34] The IRB seems to have a similar position as a Medical Ethics Committee in Europe.

The FDA will determine whether the submitted or otherwise available evidence is adequate to support a determination of safety and effectiveness of a device.

Safety
The evidence used to determine safety must adequately demonstrate "the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use". When it can be determined that the probable benefits to health from use of the device for its intended uses and conditions of use outweigh any probable risks, the benefit-risk ratio is considered acceptable.
The types of evidence used to determine the safety of a device include investigations using laboratory animals, investigations involving human subjects and non-clinical investigations including in vitro studies.

Effectiveness
When it can be determined that the device will provide clinically significant results, for its intended uses and conditions of use, in a significant portion of the target population, the device is considered effective.
The evidence used to determine the effectiveness of a device consists principally of well-controlled investigations. [35]

5.3.2 Europe

As a general rule, confirmation of conformity with the essential requirements concerning the characteristics and performances and the evaluation of the side effects and of the acceptability of the benefit-risk ratio, must be based on clinical

data. The evaluation of these data, referred to as 'clinical evaluation', must follow a defined and methodologically sound procedure based on:

1. A critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where:
    a) there is demonstration of equivalence of the device to the device to which the data relates, and
    b) the data adequately demonstrate compliance with the relevant essential requirements.

    OR
2. a critical evaluation of the results of all clinical investigations made
    OR
3. a critical evaluation of the combined clinical data provided in 1 and 2.

No further details are given in the MDD how to establish the equivalence. In the MEDDEV guidance document 2.7.1 Rev.3 (2009) on Clinical Evaluation, it is explained that the devices should have the same intended use and will need to be compared with respect to their technical and biological characteristics. These characteristics should be similar to such an extent that there would be no clinically significant difference in the performance and safety of the device. [36]

If a clinical investigation is performed, the manufacturer or its authorized representative has to submit a set of documents to the Competent Authorities of the member states in which the investigations are to be conducted. This set of documents should contain, among others:

- data allowing identification of the device in question,
- the clinical investigation plan,
- the investigator's brochure,
- the confirmation of insurance of subjects,
- the documents used to obtain informed consent,
- the opinion of the ethics committee concerned and details of the aspects covered by its opinion,
- the name of the medical practitioner or other authorized person and of the institution responsible for the investigations,
- the place, starting date and scheduled duration for the investigations,
- a statement that the device in question conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

No information is given on the actions to be performed by the Competent Authorities, but a MEDDEV document was published on this issue [37].

Other important sections of the provisions in the MDD are:

- The need to perform a clinical investigation with (active) implantable devices and devices in Class III, unless it is justified to rely on existing clinical data.
- The need to actively update the clinical evaluation and its documentation with data obtained from the post-market surveillance. Where post-market clinical follow-up, as part of the PMS plan for the device, is not deemed necessary, this must be justified and documented.
- If clinical data are not deemed appropriate, adequate justification for any such exclusion has to be given.
- Ethical aspects have to be considered when a clinical investigation is performed
- A clinical investigation has to be approved by a Medical Ethics Committee.

5.4 Risk management principles

5.4.1 USA

Risk management is a component of the Quality Systems Regulation for medical devices. Risk management involves:

- the identification and description of hazards
- how hazards could occur
- the expected consequences of the hazards
- estimations/assessments of the relative likelihood of the hazards

Following the identification and estimation of risks, the risk management focuses on controlling the risks. Controlling the risks is a central requirement of the Design Controls described in the Quality Systems Regulation. The quality system regulation includes requirements related to the methods used in, and the facilities and controls used for, designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical devices intended for human use. [38]

The standard EN/ISO 14971 describes the methodology for risk management for medical devices. [39] In the recognized consensus standards database of FDA, as mentioned in section 5.2.1, this EN/ISO standard is included and applies without restrictions.

5.4.2 Europe

The risk management principles are stated in the general essential requirements 1-6, indicating that risks should be reduced or eliminated as far as possible, that there should be a favorable ratio between benefits and risks/side effects during the entire stated lifetime of the device. Moreover, in essential requirement 2, the MDD requires that, 'In selecting the most appropriate solutions, the manufacturer must apply the following principles in the following order:

- eliminate or reduce risks as far as possible (inherently safe design and construction),
- where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated,
- inform users of the residual risks due to any shortcomings of the protection measures adopted.'

Moreover, the risk analysis is part of the technical documentation that a manufacturer has to compile.

EN ISO 14971 is a harmonized European standard which describes the methodology for risk management for medical devices. [39] PMS (see section 8.1) is considered to be an important element in managing the risks associated with medical devices during their entire life.

6 Mutual recognition

Once a device has obtained a CE certificate from a Notified Body in one European member state or has been self-certified by the manufacturer, it is automatically approved in the other European member states. An FDA-approved device can be marketed in the USA. The CE mark has no official status in the USA and an FDA-approved device has no official status in Europe.
Currently, Competent Authorities participating in IMDRF have created the Medical Device Single Audit Program (MDSAP). The goal of this initiative is that a single audit of a medical device manufacturer will satisfy the relevant requirements of the medical device regulatory authorities participating in the program, thus reducing the burden for the manufacturer. A pilot started in 2014, in which regulatory authorities from the USA, Canada, Brazil and Australia will participate. [40]

Since 1998, there exists a mutual recognition agreement (MRA) between USA and Europe. "This Agreement specifies the conditions by which each Party will accept or recognize results of conformity assessment procedures, produced by the other Party's conformity assessment bodies or authorities, in assessing conformity to the importing Party's requirements, as specified on a sector specific basis in the Sectoral Annexes, and to provide for other related cooperative activities. The objective of such mutual recognition is to provide effective market authorization throughout the territories of the Parties with regard to conformity assessment for all products covered under this Agreement."
This MRA does not harmonize the legislative requirements between both regions and does not apply to Class III medical devices. Under the MRA, to sell a device in Europe, a USA medical device manufacturer submits an application to a conformity assessment body (CAB) in the USA for review based on EU requirements. After conducting its review, the USA CAB recommends approval to a European CAB. Once the product is approved by the European CAB, it can be sold in the European market. Similarly, a European manufacturer who wants to sell medical products to the USAwill submit an application to a European CAB for review based on USA (FDA) requirements. This MRA allows manufacturers to use CABs in their own country, thereby lowering the burden for the manufacturer. However, the FDA will only allow CABs to conduct assessments when these CABs have shown to the FDA that they are capable of performing such an assessment. [41] [42]

Companies with a CE-marked medical device, can submit their European clinical data in the USA if the clinical design protocols are similar to those in the USA. However, data obtained from foreign clinical sites can only support the USA data, not replace it.

7 Decision making

7.1 USA

The decision to allow a device access to the market is made by the FDA, except for Class I devices, where the manufacturer is solely responsible. Moreover, manufacturers, with a few exceptions, have to fulfill the requirements for a quality system, also known as cGMP (current good manufacturing practices). The FDA can perform GMP inspections, but it is not indicated how this is done (who, why, when). In addition, it is unclear whether an FDA inspection is a prerequisite for certain types of market authorization. The requirements for cGMP are aligned, to the extent possible, with the requirements in ISO 9001 and ISO 13485 [43], which is the standard for the quality management system for medical devices manufacturers. Manufacturers have some freedom to fill in the details of their quality management system, because the requirements are not worked out in detail, as they have to apply to the wide variety of medical devices. [44]
For 510(k) submissions, seven companies are designated as accredited persons for 510(k) review, see also section 4.1. Three companies are also European Notified Bodies (BSI, Dekra, TÜV Sud North America). These companies will review the 510(k) file of the companies. The Accredited Person conducts the primary review of the 510(k), then forwards its review, recommendation, and the 510(k) to FDA. By law, FDA must issue a final determination within 30 days after receiving the recommendation of an Accredited Person. 510(k) submitters who do not wish to use an Accredited Person may submit their 510(k)s directly to FDA. [23]
If a product has not passed one of the FDA routes for access to the market, but is nevertheless marketed, the product is considered to be adulterated.

7.2 Europe

In Europe, manufacturers of Class I medical devices, which do not have a measuring function (Im) and are not marketed as sterile (Is), can follow a conformity assessment procedure (CAP), not involving a third party. However, these manufacturers have to notify themselves to the national Competent Authority, so the Competent Authorities can verify the contents of the notification. Medical devices Class Is, Im, IIa, IIb and III require the involvement of a Notified Body for the CAP. The involvement of the Notified Body increases with increasing risk class, requiring a full examination of the device design by the Notified Body for a Class III device. For medical devices of Class IIa and IIb following the CAP in Annex II, it is required that the Notified Body examines the device design of a representative sample of a device subcategory, respectively a generic device group (see also table 2). The Notified Body will issue a CE certificate for the device(s) it has assessed and the manufacturer can then legally affix a CE mark on the devices concerned. Notwithstanding the involvement of a Notified Body, the manufacturer remains ultimately responsible for the CE-marked device, even for a Class III device. Although a quality management system is not a prerequisite to obtain market authorization in Europe, in many conformity assessment procedures, a quality system is required. Moreover, the standard EN ISO 13485 [43], as mentioned above, is a harmonized standard in Europe, and is likely to be also applied by manufacturers that follow a conformity assessment procedure not requiring a quality management system, e.g. Class I manufacturers. As a Notified Body will

periodically inspect a manufacturer, the activities of the manufacturer, ensuring that he conforms to the requirements, will be checked.

8 Post-marketing requirements

8.1 Vigilance and post-market surveillance

8.1.1 USA

Manufacturers have to report to the FDA incidents and events requiring remedial action to prevent an unreasonable risk of substantial harm to the public health. The FDA can request additional information of the manufacturer if this is deemed necessary to safeguard public health. FDA requires that a "good faith effort" is made by the manufacturer to obtain information about the event. [45]
Manufacturers are required to report to FDA when one of their marketed devices has or may have caused or contributed to a death, serious injury, or has malfunctioned, and that the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. The manufacturer shall evaluate whether or not an event is reportable. [46]
Furthermore, FDA may order PMS studies to be conducted as a condition for PMA approval. FDA can order such studies at the time of approval or at any time thereafter for any approved device if any of these circumstances are met:

- the failure of the device would be reasonably likely to have serious adverse health consequences; or
- the device is intended to be implanted in the human body for more than one year; or
- the device is expected to have significant use in pediatric populations; or
- the device is intended to be a life sustaining or life supporting device used outside a device user facility.

There is a website listing all PMS studies that are undertaken. [47] [48]

Device user facilities (i.e. hospitals, ambulatory surgical facilities, nursing homes, outpatient diagnostic facilities, or outpatient treatment facilities, which are not a physician's offices) are required to report:

- device related deaths to the FDA and the device manufacturer;
- device related serious injuries to the manufacturer, or to FDA if the manufacturer is not known; and
- submit to FDA on an annual basis a summary of all reports submitted during that period. [49]

For several devices (e.g. Silicone Gel-Filled Breast Implants), FDA requires manufacturers to track these devices from their manufacture through the distribution chain. [50]

8.1.2 Europe

The MDD requires manufacturers, irrespective of the device class, to "institute and keep up to date a systematic procedure to review experience gained from devices in the post-production phase, including the provisions referred to in Annex X, and to implement appropriate means to apply any necessary corrective action". This obligation to review experiences gained with a medical device is usually known as pPMS. It is not stated how the experiences have to be collected. Examples of information sources are complaints, literature, customers surveys. It should be noted that it is required that the clinical evaluation has to be updated with "data obtained from the post-market-surveillance".

This systematic procedure must include "an obligation for the manufacturer to notify the Competent Authorities of the following incidents immediately on learning of them:

1. any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the instructions for use which might lead to or might have led to the death of a patient or user or to a serious deterioration in his state of health;
2. any technical or medical reason connected with the characteristics or performance of a device leading for the reasons referred to in subparagraph (i) to systematic recall of devices of the same type by the manufacturer."

The obligation to notify the authorities in case of incidents and taking appropriate action is known as a vigilance system. This is further elaborated upon in the MEDDEV guidance document of a medical device vigilance system. [51] Examples of corrective action that can be required following an incident are:

- a device recall
- the issue of a field safety notice
- additional surveillance/modification of devices in use
- modification to future device design, components or manufacturing process
- modification to labelling or instructions for use

There is no requirement in the MDD that users should report incidents, either to the Competent Authorities or to the manufacturer. There can be national legislation, requiring users (i.e. healthcare institutions, professionals, carers or patients using or maintaining medical devices) to report incidents with medical devices to the manufacturer or the National Competent Authority. For example the requirements in the Dutch Health Institutions Quality Act ("Kwaliteitswet Zorginstellingen") [52] resemble the requirements in the USA, although this is broader than medical devices and concerns care-related incidents.
The MDD does not contain specific requirements for traceability of medical devices. However, the standard EN ISO 13485 [43] specifying requirements for the quality management system for manufacturers of medical devices, traceability is addressed. For implantable medical devices it is even specifically required. In 2013, Commission Recommendation 2013/172/EU on a common framework for a unique device identification (UDI) system of medical devices was issued as an important step towards ensuring effective traceability of medical devices in the Union. [53]

8.2 Distribution and sales channels

8.2.1 USA

Manufacturers (both domestic and foreign) and initial distributors (importers) of medical devices must register their establishments with the FDA. This provides FDA insight into the distributions channel. [54]

8.2.2 Europe

There are no requirements for the distribution or sale of medical devices in the MDD, apart from a general statement: "Member States shall take all necessary steps to ensure that devices may be placed on the market and/or put into service only if they comply with the requirements laid down in this Directive when duly supplied and properly installed, maintained and used in accordance with their intended purpose."
Moreover, only manufacturers of Class I and custom made devices, parties assembling systems and procedure packs and parties performing reprocessing are required to register themselves with the national Competent Authorities.

This provides limited information on the market of medical devices. The European EUDAMED database can improve the availability of the information in Europe. However, due to its incomplete use, the value of that database is limited (see also section 3.3.2).

8.3 Supervision and recall

8.3.1 USA

The FDA can perform inspections at the manufacturer's site, although no guidelines on the reasons and frequency of these inspections could be found. A recall is often voluntarily initiated by the manufacturer, although a recall can also be initiated by the FDA to protect public health or as a consequence of serious deceit. A recall always has to be notified to the FDA and the data related to the recall will be made public.

8.3.2 Europe

After CE certification the EU member states are responsible for ensuring that the medical devices, when correctly installed, maintained and used for their intended purpose, do not compromise the health and/or safety of patients, users or other persons. Incidents (malfunction, deterioration in performance, technical or medical issues related to the performance) must be notified to the relevant national Competent Authorities by the manufacturer or the Authorized Representative. A recall is often initiated by the manufacturer itself. The Competent Authority will monitor this process. If a manufacturer does not withdraw a device from the market, a member state can withdraw a device from the market, or prohibit or restrict its marketing authorization. In this case, the Commission must be informed immediately. The Commission will consult all parties involved and inform all member states when the measures are justified.

8.4 Changes and variations

8.4.1 USA

After FDA has approved a PMA, an applicant must submit a PMA supplement for review and approval by FDA before making any change affecting the safety or effectiveness of the device. [55]
For a 510(k) cleared medical device, the nature and extent of the change to a device determines whether or not a new 510(k) has to be submitted. There is a guidance document available to help manufacturers with that decision. [56]
No maximum validity period was found for the market authorization of medical devices in the USA.

8.4.2 Europe

When a Notified Body was involved in the market approval of a medical device, the Notified Body must be informed of any plan for changes to either the quality system or the device. For a Class III device, the Notified Body must be informed about every change to the approved design. If a range of products is covered by a CE certificate, mainly following the procedure in Annex II of the MDD, the Notified Body must be informed about substantial changes to one or more of the devices covered. It is up to the manufacturer to decide if a change is substantial. The Notified Body must assess these changes and decide on acceptability.
A certificate issued by a Notified Body has a maximum validity of 5 years, after which the certificate can be renewed following a full re-assessment. The MDD requires the Notified Body to periodically (usually yearly) carry out appropriate inspections and assessments during the validity period of a certificate to assess continued compliance.

9 Transparency

9.1 Decision bodies

9.1.1 USA

The FDA is the authority for approval of market authorization for medical devices.

9.1.2 Europe

Notified Bodies for medical devices are designated by the member state in which they are based. There can be more than one Notified Body per member state. The European Commission has published a list of all designated Notified Bodies, including the categories of medical devices for which they have been designated. [57]
When a Notified Body has been withdrawn or the authorization has expired, this is also noted in this list. However, the reason for withdrawal is not given.
A manufacturer is free to choose a Notified Body, the Notified Body does not have to be based in the same country as the manufacturer. The Notified Body involved is always indicated on the label of a medical device, in conjunction with the CE mark.

9.2 Time frames for approval

9.2.1 USA

Timeframes are given for the FDA to process PMA approvals (180 days) and 510(k) approvals (90 days). However, the timeframe does not include the time needed to reply to FDA's questions. FDA does not always meet the required timeframes. [58]

9.2.2 Europe

In the medical device legislation no specific procedure time is mentioned. In practice clients can negotiate with the Notified Body involved on how long it will take to obtain a decision on authorization.
A timeframe of 210 days is laid down for the scientific opinion of the medicines evaluation boards/EMA for medical devices containing medicinal products.

9.3 Authorization status of products

9.3.1 USA

There is no mark to identify an approved device. However, databases are available in which approved devices can be found.

9.3.2 Europe

A device that has successfully gone through a conformity assessment procedure shall carry the CE mark. If a Notified Body was involved in the conformity assessment procedure, the manufacturer will be given a so-called CE certificate, that a specific device or group of devices fulfills the requirements in the MDD. If applicable, the identification number of that Notified Body shall accompany the CE mark. As the certificates contain the information on the assessments by the Notified Bodies and the devices concerned, these data should be centrally available. The EUDAMED database has a module on certificates, but due to the fact that this system is not widely used, these data are not complete and not

reliable. Moreover, the (limited) information in EUDAMED database is only accessible for Competent Authorities (see also section 3.3.2).

9.4 User information

9.4.1 USA

"Adequate directions for use" means directions under which the layman can use a device safely and for the purposes for which it is intended. The following items are considered important parts of directions for use and need to be adequately specified:

a) Statements of all conditions, purposes, or uses for which such device is intended, including conditions, purposes, or uses for which it is prescribed, recommended, or suggested in its oral, written, printed, or graphic advertising, and conditions, purposes, or uses for which the device is commonly used; except that such statements shall not refer to conditions, uses, or purposes for which the device can be safely used only under the supervision of a practitioner licensed by law and for which it is advertised solely to such practitioner.
b) Quantity of dose, including usual quantities for each of the uses for which it is intended and usual quantities for persons of different ages and different physical conditions.
c) Frequency of administration or application.
d) Duration of administration or application.
e) Time of administration or application, in relation to time of meals, time of onset of symptoms, or other time factors.
f) Route or method of administration or application.
g) Preparation for use, i.e., adjustment of temperature, or other manipulation or process. [59]

It is remarkable that the FDA considers instructions for use as adequate, when they can be understood by lay persons, whereas in Europe, the type of user (e.g. lay or professional) shall be considered when designing a product and therefore also when drafting the instructions for use. Only for IVDs for self-testing, there is an explicit requirement that the instructions for use have to be acceptable for the use by lay persons and even requires the involvement of a Notified Body.

A device which is not safe except under the supervision of a practitioner licensed by law to direct the use of such a device, and hence for which "adequate directions for use" cannot be prepared, does not have to fulfill the requirements for labeling. It should however display the following caution: Federal law restricts this device to sale by or on the order of a_____". The blank can be filled with "physician" or "dentist". [60]

9.4.2 Europe

The MDD contains a listing of general requirements for labels and instructions for use. The MDD allows member states to require the information to be supplied with a medical device 'to be in their national language(s) or in another Community language, when a device reaches the final user, regardless of whether it is for professional or other use.' For the Netherlands, Dutch instructions for use need to be supplied with a medical device. Since 11 April 2014, using the English language is accepted for professional users of medical devices, when these users have adequate command of the English language, whereas beforehand, an exemption had to be requested and was only granted in specific cases. [61]

9.5 8.5 Information on vigilance issues

9.5.1 USA

FDA publishes consumer information about the most serious medical device recalls. Also, FDA publishes safety communications, providing users with relevant information on serious problems with medical devices. The information on incidents reported to the FDA is publically available on the FDA website. [62]

9.5.2 Europe

No information on vigilance issues is centrally and publicly available. National Competent Authorities can make information available and exchange with other authorities the vigilance reports through a mailing list on a voluntary basis. The European database on medical devices (EUDAMED), which is not yet fully implemented, should contain information on vigilance issues. It is not envisaged that all information in EUDAMED will become publicly available.

10 Discussion

10.1 Comparison of systems in USA and Europe

Both in the USA and in Europe, legislation has been implemented to guarantee the availability of safe and effective medical devices. Comparing the market authorization procedures of the USA and Europe revealed that the basic concepts are similar. In both systems, the effort to obtain market authorization increases with the perceived risk of a device, and in both systems equivalence to an existing device on the market enables easier market authorization. On the other hand, also differences between the systems can be identified. An important difference is that market authorization in the USA is granted by the FDA and is thus a governmental responsibility, while in Europe market authorization is granted by companies designated and supervised by the authorities.
In both systems, the technical requirements are not specified in detail in the legislation itself, which either contains only generally stated essential requirements or does not state any requirements. In Europe, harmonized European standards detailing technical specifications and requirements are a legislative tool for manufacturers to demonstrate conformity with the essential requirements. The European Commission does not participate in the development of the standards. However, they employ so-called CEN consultants to check the correctness of the Annexes Z in the standards, which indicate the presumption of conformity that can be claimed by using the standard by linking clauses in the standard to the essential requirements (see also section 5.2.2). This allows them to have some indirect influence. In the USA, recognized consensus standards can be national or international standards. The FDA decides if standards become recognized standards and to what extent, which provides FDA with the possibilities to influence the technical requirements for medical devices. Moreover, the FDA participates in the development of standards, which allows them to influence the content of the standard. Some European member states also participate in developing standards, e.g. the Netherlands and Sweden.

The FDA has indicated several times that the USA system is better than the European system in providing safe and effective medical devices to the market. In its 2012 report "Unsafe and Ineffective Devices Approved in the EU that were Not Approved in the US", the FDA portrays 12 medical devices that were marketed in Europe, but not in the USA, and for which problems were found, often during clinical investigations to obtain PMA clearance. [63] Among these 12 devices are an elbow implant, which was predicted by FDA - and in practice shown - to be prone to fractures and a non-invasive method to measure blood glucose levels. Although these examples indicate a positive effect of the high requirements of the FDA on clinical investigations on safety and performance/clinical value, the downside is that on average, it takes two years longer to get a device approved in the USA. [64] This could mean that a life saving device is withheld from US patients, whereas it is available to European patients. This even leads to American citizens going abroad to get a specific medical treatment. Also, companies choose to first introduce their device on other markets than the USA or even contemplate not introducing specific devices in the US. In this context, it should be noted that only approximately 1% of all devices granted market authorization in the USA require PMA submission. [15] Therefore, the majority of the devices on the US market will have followed the

equivalence route (510(k)) or did not require the submission of documentation to the FDA at all (Class I).
Another issue to consider in relation to the time it takes to bring a medical device to the market is the short life cycle of medical devices. It is generally accepted that a medical device life cycle can be as short as two years. [65]
The FDA also explicitly pointed out that Notified Bodies are private companies, hinting that this is inferior to a governmental institution. To put this into perspective, it should be noted that a number of medical devices for which problems occurred, and which have been widely covered in the news media, like the pacemaker leads, metal-on-metal hip implants and transvaginal meshes, were available both in the USA and in Europe. For the pace maker leads, a Class III product, placed on the market through the PMA procedure, the clinical study duration was not sufficiently long to establish the vulnerability of these leads over time. This kind of cases where products on the market led to major problems for patients, have shown that both systems are not perfect.
It is important to also highlight the balance that a regulatory system has to achieve between safety and availability of innovative products. A report by the Boston Consultants Group investigated the number of recalls in both USA and Europe. [66] They concluded that the number of serious recalls was very similar in both situations and also the reasons for the recalls (e.g. manufacturing or design) were similar. Therefore, it was concluded that the level of safety provided by both systems is not really different.

In Europe, several metal-on-metal hip implants were granted access to the market using no or limited self-generated clinical data and claiming equivalence to other metal-on-metal hip implants, arguing that safety and performance were at least comparable. [67] In the USA, such products were allowed on the market based on the principle of equivalence, meaning they only had to provide data with regard to equivalence of both devices, and no additional data regarding their own device. This clearly highlights the problem of establishing equivalence, which is clearly not unique to the EU system. See also the comment on the 510(k) procedure (section 11.3).

Although the requirements are different in both systems, it cannot be stated, based on the requirements, that one system will lead to a different level of quality and safety than the other when correctly applied.

10.2 Comments on and future of European legislation

In Europe, the need to revise the medical device legislation was felt for a longer period, but the discussion on this revision intensified following the PIP breast implant scandal and was further fed by the incidents with metal-on–metal hip implants and transvaginal mesh implants. In September 2012, the European Commission published the proposal for the new Medical Devices Regulation. Major issues identified in the current legislation, such as the variability between Notified Bodies and the need for more clinical studies are addressed in this proposal. Furthermore, a more rigorous procedure is proposed for Class III medical devices. In the proposed new regulation, there is a pivotal role for one or more databases in which a variety of information on medical devices, including vigilance data, are collected. The feasibility of such a database is questionable, considering the current limited use of the European medical device database EUDAMED, although this hesitation in the use of EUDAMED might be linked to the prospect of implementing another version of the system in the near future, when the new medical device legislation will come into force. It is unclear when the final version of the regulation will be published, although 2015 seems

unlikely. The changes proposed increase the involvement of the Notified Bodies, increase the involvement of the national Competent Authorities in market surveillance activities and makes the conformity assessment procedures more elaborate. The system will thereby go beyond improving the points identified as needing improvement, most likely as a consequence of the public outrage over the high profile cases like the PIP breast implants.
As a consequence of the PIP case, the Notified Body involved in the conformity assessment procedure for that product has been sued by the patients that have been implanted with these devices. This claim by the patients was sustained, which indicates that the judge considers that not only the manufacturer can be held responsible for the product. According to the court, the Notified Body had "neglected its duties of checking and vigilance" by certifying that the PIP implants conformed to safety rules. The Telegraph (14 November 2013) also mentions that suing the Notified Body was the women's only chance of financial compensation, because the French firm of PIP is no longer solvent. [68]
The idea of PMS is that this is an element of the manufacturer's activities, in which he actively collects experiences with medical devices after they have been placed on the market. Actively collecting indicates that this is more than just reacting on customer complaints. Experiences with the medical device shall be actively collected from various sources and if necessary, these shall be evaluated in the risk management process and could lead to changes in the design of the product, for which experiences are again collected, thus creating a continuous cycle of improvement. [69] This active approach was not included explicitly in the 2012 proposals for new regulations by the Commission, but subsequently, proposals have been submitted to include a more active approach, especially by the Dutch delegation.
Especially since the high profile media coverage of problems with implantable medical devices, several initiatives have been taken to improve the system at short notice (ref PIP Action Plan, regulations oversight Notified Bodies and activities Notified Bodies). Recently a report was issued by the European Commission, evaluating the efforts to restore confidence in the system since the PIP joint action plan was launched. [70]

10.3 Comments on and future of USA legislation

The 510(k) process is being criticized from two sides. Some policy makers and patients have expressed concern about the ability of the 510(k) process to ensure that medical devices on the market are safe and effective. On the other hand, there are policy makers, patients, as well as medical device industry, that find that the 510(k) process has become too burdensome and time-consuming and thus it is delaying important new medical devices from the market.
A major reason for considering the 510(k) process as being too weak, is that several types of Class III devices can still obtain market clearance through the 510(k) process, as the predicate devices were already available before the Medical Device Amendments came into force in 1976. A well-known example is the metal-on-metal hip replacement. The FDA has asked the Institute of Medicine (IOM) to investigate the 510(k) process and this institute concluded in 2011 that the use of the 510(k) process for Class III devices does not provide "reasonable assurance of safety and effectiveness" although this is a legal requirement, before a device is marketed. The reason for this discrepancy is that in general safety and effectiveness do not have to be substantiated in a 510(k) submission, but only the equivalence to the predicate device needs to be substantiated, after which the device is assumed to be as safe and effective as the predicate device. The IOM recommends the development of an integrated pre-market and post-market legislative framework. [71] This emphasis on post-

market requirements indicates that this issue, which is already addressed in Europe, will also become more prominent in the USA.
Also another institute, the United States Government Accountability Office, GAO, has identified this shortcoming in the 510(k) process in 2009 and advised the FDA to "expeditiously take steps to issue regulations for Class III device types currently allowed to enter the market via the 510(k) process by requirement of PMAs or reclassifying them to a lower class". [72]
The FDA has published draft guidance for evaluating substantial equivalence in 510(k) notification. It is feared by manufacturers that this guidance will lead more often to a non-SE decision and therefore leading to more *de novo* procedures. Moreover, as FDA can request more information from the manufacturer in a *de novo* procedure, this procedure is sometimes considered to be "PMA-lite". [73]

It is often argued that FDA takes longer to process 510(k), *de novo* or PMA submissions. The GAO has investigated this matter and found that FDA did not meet all of its timelines. For 510(k), the required timelines are quite often met, whereas this is less often the case for PMA submissions. However, the time calculated by FDA does not include the time taken by the company to collect and submit the information requested by FDA during review. If the total elapsed time for initial submission to final decision is considered, this time period has increased. [58]

Another issue with the FDA is the lack of predictability and consistency in the reviews. The Makower report [64] indicates that key persons change during the review and key persons are not always present during important meetings. This could be one of the reasons for medical device manufacturers to judge the FDA as lacking predictability and consistency.
Another reason for the lack of predictability and consistency could be the absence of specific requirements for particular medical devices, which makes the assessment more dependent upon the knowledge and experience of the FDA assessor(s).

11 Conclusions

Comparing the market authorization procedures of the USA and Europe revealed that the basic concept of the legislation is similar. In both systems, the effort to obtain market authorization increases with the perceived risk of a device. Furthermore, easier market authorization can be obtained if equivalence to an existing device on the market can be claimed and in both systems, market access for the lowest risk class devices is the sole responsibility of the manufacturer.

Differences between the systems are:

- In the USA, market authorization is granted by a governmental agency, whereas in Europe this responsibility has been delegated to designated companies.
- The large variation in time to the market in Europe and the USA, mainly for the highest risk devices, which appears to be due to the stricter requirement to perform more elaborate clinical studies for medical devices going through the PMA procedure in the USA.
- Only 1% of all medical devices granted market authorization in the USA requires a PMA submission (the most stringent procedure).
- There is no explicit requirement for post market surveillance in the USA legislation, although the FDA can require this for specific devices.
- The essential requirements for products are well described in the EU legislation, whereas this is less clear in the USA.
- The FDA makes most information on medical devices, related to market authorization and post-market activities publicly available, whereas such transparency does not exist in Europe.
- The way of classification of medical devices and possible changes to established classifications.

It cannot be stated, based on the requirements, that one system will lead to a different level of quality and safety than the other when correctly applied. For both systems, work is going on to consider opportunities to strengthen the system, especially in Europe, since new legislation is under development there.

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