How to place human medical devices on the market? An overview and critical examination of the regulatory requirements in Germany versus those in the United States

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List of Abbreviations

AIMDD	COUNCIL DIRECTIVE 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to *active implantable* medical devices
BfArM	Federal Institute for Drugs and Medical Devices
BMG	Federal Ministry of Health
CDRH	Center for Devices and Radiological Health
CEN	European Committee for Standardization
CENELEC	European Committee for Electrotechnical Standardization
CFR	Code of Federal Regulations
cf	Latin: confer, "compare"
CMDCAS	Canadian Medical Device Conformity Assessment System
DIMDI	German Institute of Medical Documentation and Information
DIN; EN; ISO	German Institute for Standardization; European Standards; International Organization for Standardization
EC	European Community
EEA	European Economic Area
EEC	European Economic Community
ElektroG	Act Governing the Sale, Return and Environmentally Sound Disposal of Electrical and Electronic Equipment
EU	European Union
(F)FD&C Act	(Federal) Food, Drug and Cosmetic Act
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
HDE	Humanitarian Device Exemption
HUD	Humanitarian Use Device
IDE	Investigational Device Exemption
IVDD	DIRECTIVE 98/79/EC of the European Parliament and of the COUNCIL of 27 October 1998 on *in vitro* diagnostic medical devices
MD	Medical Device
MDD	Medical Device Directive
MPG	Law on Medical Devices
MPKPV	Decree on Clinical Trials with Medical Devices
MPSPV	Decree on a Medical Device Vigilance System
MPV	Decree on Medical Devices
MPVerschrV	Decree concerning the Availability on Prescription only of Medical Devices
MPVertrV	Decree on Distribution Channels for Medical Devices
PDP	Product Development Protocol
PMA	Premarket Approval
QSR	Quality System Regulation
SSED	Summary of Safety and Effectiveness Data
STED	Summary Technical Document
US	United States
USA	United States of America
ZLG	Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices

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1 Introduction

Manufacturers of medical devices need to know and follow specific legal and regulatory requirements if they want to place their devices on the German or United States market. Both, Germany and the USA, have their own distinct regulatory requirements that must be met prior to a manufacturer placing their medical device on the market.

Germany as participant of the European Union is subject to the European Economic Area (EEA)[1] law. On the European Union level the Medical Device Directive (COUNCIL DIRECTIVE 93/42/EEC, known as MDD) of 14 June 1993 is the most essential of three main regulations. The COUNCIL DIRECTIVE 93/42/EEC covers a broad range of medical devices and defines requirements for marketing of medical devices. Important goals of the MDD are harmonization of medical device related rules, elimination of trade barriers and protection of community safety.

To implement the MDD, Germany transposed the MDD into national law. The Law on Medical Devices was first issued on August 07, 2002 and lastly amended on November 08, 2011. Supplementary decrees complete the Law on Medical Devices in implementing the European law within the national level.

Various competent authorities are responsible for medical devices in Germany. At political level mainly the Federal Ministry of Health (BMG) and at Länder level relevant supreme Länder authorities fulfill lawgiving functions and supervisory control of medical devices. At implementation level the Federal Institute for Drugs and Medical Devices (BfArM) is the responsible higher federal authority for medical devices. The BfArM´s duties are defined in the Law on Medical Devices § 32 no.1 and cover various functions (e.g., device vigilance system, risk evaluation, clinical trial approval). A further important authority at federal level is the German Institute of Medical Documentation and Information (DIMDI) which supports the market surveillance of devices by medical device data bases. At Länder level

[1] EEA: European Union (EU), plus Iceland, Liechtenstein, Norway and Swiss. Please note: Within this master thesis “EU” (European Union) automatically includes EEA.

relevant surveillance authorities are fulfilling the functions of general market surveillance (e.g., law-abiding performance). Which authority the responsible market surveillance authority at Länder level is, depends on Länder specific regulations. Unlike the BfArM, the responsible Länder authorities have the power to order actions to manufacturers of medical devices, if necessary to remove risks of medical devices. A further important authority at Länder level is the Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices (ZLG)[2]. The main function of the ZLG in relation to medical devices is the designation, recognition and supervision of the Notified Bodies on behalf of the federal Länder. Furthermore, the authority is the central coordination point for the surveillance of medical devices (cf. Zentralstelle der Länder für Gesundheitsschutz bei Arzneimitteln und Medizinprodukten, 2013). Article 16 of the MDD defines the functions of the Notified Body. A notified body is an independent for-profit certification organization that is designated and certified by the national competent authority (e. g, the ZLG) to perform the procedures of the conformity assessment as defined in Article 11 of the MDD and specified in the Annexes II to VII of the MDD. Aim of the successful conformity assessment is the CE-certificate[3] that shows compliance of a medical device with the legal requirements.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) is federal law and the basic regulation for medical devices. The FD&C Act establishes the power of the Food and Drug Administration (FDA) agency in relation to the supervision over medical devices. The FD&C Act is enforced by the Code of Federal Regulations (CFR). These legally binding rules and regulations, also named administrative law, regulate the most of the medical devices within the 21 CFR Part 800 - 1299 (cf. Thomson Reuters IDRAC [2], 2013).

The FDA, empowered by federal law to create and enforce rules and regulations, is part of the U.S. Department of Health and Human Services and is comprised of four divisions: (1) Medical Products and Tobacco, (2) Foods, (3) Global Regulatory Operations and Policy, and (4) Operations (cf.

[2] Please note: In other EU member states the competent authorities designating the notified bodies are settled not at Länder (federal) level like Germany but at governmental level. This is a German specialty.
[3] Also known as EC-certificate

Food and Drug Administration [1], 2012). The Center for Devices and Radiological Health (CDRH) which is under the Medical Products and Tobacco division is responsible for the regulation of medical devices. For more information on FDA organization please refer to **Appendix A**.

Except for certain exclusions, prior to a medical device being first placed on the market within the European Economic Area (EEA) which includes Germany, it must bear the CE marking (cf. European Parliament and Council, 1993) and, where required with reference to the conformity assessment, the identification number of the Notified Body. With affixing the CE marking on the device and the declaration of conformity the manufacturer declares on his sole responsibility that the device is in conformance with the applicable legal requirements, that it fulfills the essential requirements as defined by the Directives ergo by the community of the EU and that the conformity of the device was examined by an independent Notified Body. The CE marking is also required to devices made in other countries but marketed in the EEA.

For products marketed in Germany, the German competent authority is responsible for ensuring that only CE-marked devices are distributed and that devices which are non-conforming to the essential requirements are withdrawn from the market. In Germany, only custom-made devices, devices used in clinical trials and in house production devices according to the Law on Medical Devices (MPG) §3 no.21, In-vitro diagnostics for performance assessment and devices according to § 11 no.1 of the MPG do not require CE marking (cf. Bundesministerium der Justiz, 2012).

To receive CE marking the device must be assessed during a conformity assessment that depends on the class of the device. For devices with medium and high risk, a designated independent third party known as a “Notified Body” must be involved in the conformity assessment. In contrast to the German Marketing Authorization of medicinal products a pre-market approval issued from a German competent authority (e.g., the BfArM) is not required for Germany.

Unlike in Germany, the USA market does not allow a conformity assessment through a notified body. Instead, a pre-market authorization is required prior to a medical device being first placed on the market in the USA. The pre-

market authorization will be issued by the United States Food and Drug Administration (FDA), a regulatory authority in the USA. Basically there are two different types of device authorizations which allow a device to be fully marketed in the USA; the 510(k) Premarket Notification and the Premarket Approval (PMA) (cf. Food and Drug Administration [2], 2012). Which process that is used depends on the device classification (cf. Food and Drug Administration [2], 2010). Only medical devices that are exempted from any authorization procedures need neither 510(k) device clearance nor PMA approval. In addition, medical devices that treat or diagnose rare conditions or diseases and which fall under the Humanitarian Use Device (HUD) definition in 21 CFR[4] 814.3(n) can, after the HUD application is designated, submit a Humanitarian Device Exemption (HDE) marketing application (cf. Food and Drug Administration [1], 2010).

In contrast to the German labeling requirements as per Article 17 of the MDD, no special marks on the labeling are required to indicate FDA clearance (510(k)) or FDA approval (PMA) for the US market. Nothing is on the labeling or outer packaging which shows the 510(k) number or the PMA number. The system in the USA is such that if a company is selling a medical device it must have been cleared for sale by the FDA unless it is exempt from clearance due to its low risk or falls under an Investigational Device Exemption (IDE) and is marked with an IDE sticker as required per 21 CFR Part 812.

The present master thesis provides a regulatory overview of the current ways on how to place a medical device on the German market and on the US market. The thesis also critically examines regulatory differences between both countries. Beginning with a short introduction of both country legal frameworks, the thesis then gives attention to the specific regulations. Important pre- and post-market requirements and other considerations will be addressed. The critical examination starts with the discussion of the regulatory framework then, the quality system and the device classification

[4] CFR: The CFR is a codification of the general and permanent rules that were published in the FR by the Executive departments and agencies of the Federal Government. It is divided into 50 titles that represent broad areas subject to Federal regulation (cf. US Government Printing Office, 2013).

system will be discussed before the options gaining market access as well as the pre- and post-market requirements will be examined.

2 Regulatory framework

2.1 Regulatory overview - Germany

Germany as a member of the European Union is subject to the European Economic Area law. On the European Union level the core regulations for the marketing of medical devices consists of three main Directives:

1. COUNCIL DIRECTIVE 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to *active implantable* medical devices, as last amended by DIRECTIVE 2007/47/EC, known as AIMDD
2. DIRECTIVE 98/79/EC of the European Parliament and of the COUNCIL of 27 October 1998 on *in vitro* diagnostic medical devices as last amended by Regulation 1882/2003 and Regulation 596/2009, known as IVDD; and
3. COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning *medical devices*, as last amended by DIRECTIVE 2007/47/EC, known as MDD.

The COUNCIL DIRECTIVE 93/42/EEC is an important overall Directive as it covers a broad range of medical devices and defines requirements for their marketing. To implement the MDD, Germany transposed the MDD into national law. The Law on Medical Devices was first issued on August 07, 2002 and lastly amended on October 19, 2012 (cf. Bundesministerium der Justiz, 2012). Additionally, the following main decrees complement the Law on Medical Devices in implementing the European law within the national level (cf. Thomson Reuters IDRAC [1], 2013):

- Decree on Medical Devices (MPV);
- Decree on a Medical Device Vigilance System (MPSPV); and
- Decree on Clinical Trials with Medical Devices (MPKPV).

Germany basically complies with the marketing requirements of the European legislation (cf. Thomson Reuters IDRAC [1], 2013) therefore the present master thesis refers to the MDD requirements. Special German marketing requirements are separately discussed in Chapter 10.5.

All three medical devices Directives are harmonized Directives, based on the 'New Approach' concept. The 'New Approach' concept for product regulation is defined in the COUNCIL RESOLUTION of 7 May 1985 on a new approach to technical harmonization and standards (85/C 136/01) in addition with the global approach to certification and testing[5] and COUNCIL DECISION 90/683/EEC[6] (cf. EUROPEAN COMMISSION, 1999). The new and the modular approach were revised in 2008 to the "New Legislative Framework" that was adopted in COUNCIL on July 09, 2008[7] (cf. EUROPEAN COMMISSION [1], 2013).

The idea behind the new and modular approach is to eliminate barriers to trade[8] and to protect public safety through the harmonization of technical regulations.

Product Directives which are based on the 'New Approach' define the essential requirements with regard to safety, performance and health protection of a product but do not substantiate the technical specifications for their performance. Therefore, harmonized technical standards issued from European standardization organizations (e.g., CEN, CENELEC) specify the required technical provisions and provide guidance to manufacturers.

Medical device manufacturers are free to use the harmonized standards to demonstrate that their medical device performs to the requirements of the essential requirements[9]. They may also use their own product specifications, non-harmonized standards or any other technical solution, but then they need to prove that their device meets an equal level of safety as with the use of a harmonized standard. However, with the application of a harmonized standard during design and manufacturing of a medical device a presumption

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[5] COUNCIL RESOLUTION of 21 December 1989 on a global approach to conformity assessment (90/C 10/01)

[6] COUNCIL DECISION 90/683/EEC was replaced by COUNCIL DECISION 93/465/EEC; 93/465/EEC was replaced by DECISION 768/2008/EC in 2008 due to the revision of the 'New Approach'.

[7] For more details please refer to: Single market for goods **'New legislative framework' for marketing of products** http://ec.europa.eu/enterprise/policies/single-market-goods/internal-market-for-products/new-legislative-framework/; Last update: 05/02/2013

[8] For example, companies were used to have to request regulatory approval from each country in Europe prior marketing of devices prior to the 'New Approach' concept.

[9] According to the MDD in Annex I the essential requirements are the needs a device must fulfill to have a high level of protection of health and safety available. Therefore, Annex I of the MDD states the requirements that must be considered during design and manufacturing of the device.

of conformity is given assuming that all essential requirement needs are fulfilled (cf. European Parliament and Council, 1993). The MDD describes the use of harmonized standards in Article 5. The performance of the medical devices to the essential requirements will be assessed during a conformity assessment, in many cases through the Notified Body[10] designated by the Competent Authority (Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices (ZLG)[11]). The end point of a successful conformity assessment is the CE marking of the device as described in Article 17 of the MDD. Once a medical device has been CE-marked it can be distributed throughout the EEA (cf. European Parliament and Council, 1993).

The purpose of the 'Modular Approach[12]' which is adopted through the harmonized Directives is to describe harmonized instruments for a global approach for the assessment of conformity and the requirements for the CE marking. The approach defines eight modules for conformity assessment (cf. European Parliament and Council, 2008). On the basis of the modules, various forms of the conformity assessment procedure can be generated. Certain modules can be performed by the manufacturer itself, but some modules have to be carried out involving a notified body, an independent for-profit organization that is designated and certified by the national competent authority (e. g., the ZLG) to perform the procedures of the conformity assessment. The determination, of which conformity assessment procedure within the MDD can be used, depends on the kind of product and its risk.

2.2 Regulatory overview – The USA

The Federal Food, Drug, and Cosmetic Act, a set of federal laws published in the United States Code, was signed into law in 1938 (FD&C Act) and is the basic regulation for medical devices. The FD&C Act was developed and issued by the US Congress (Legislative branch) and was signed by the

[10] The Notified Body is an independent for-profit organization who is designated and certified by the national Competent Authority to perform the procedures of the conformity assessment as specified in the Annexes of the MDD (Please also refer to MDD Article 16).

[11] Please note: In other EU member states the competent authorities designating the Notified Bodies are settled not at Länder (federal) level like Germany but at governmental level. This is a German specialty.

[12] also called Global Approach

President (Executive branch). The FD&C Act consists of twenty Chapters that are legally binding to the FDA and Industry and is effective until modified or expired. Medical devices are regulated in Chapter V.

Significant medical device regulating amendments to the FD&C Act are (cf. Thomson Reuters IDRAC [2], 2013):

- Medical Device Amendments of 1976
- Safe Medical Devices Act of 1990
- Medical Device Amendments of 1992
- FDA Modernization Act of 1997
- Medical Device User Fee & Modernization Act of 2002
- Food and Drug Administration Amendments Act of 2007
- Food and Drug Administration Safety and Innovation Act of 2012

The Federal Government of the United States consists of three branches: the Legislative, the Judicial and the Executive. The FDA is part of the Department of Health and Human Service which is a cabinet department in the executive branch. Duties and responsibilities of the Executive branch are to execute and enforce the federal laws of the US. On the basis of the FD&C Act the FDA develops legally binding rules and regulations which further specify and detail the implementation of the requirements of the FD&C Act. To issue the FDA rules and regulations, the FDA must comply with the procedures stipulated by the Administrative Procedure Act (cf. Food and Drug Administration [3], 2010). Regulations and rules for medical devices issued by the FDA are enforceable federal laws authorized by major legislation enacted by Congress and approved by the President (cf. Marjorie Shulman, kein Datum). Such regulations and rules are known as Code of Federal Regulations (CFR) and consist of general and permanent rules that have been developed from various departments and agencies of the Federal Government and that have been published in the Federal Register (cf. US Government Printing Office, 2013). The CFR contains 50 titles regulating a broad range of affairs which are subject to Federal regulation and which are updated annually (cf. US Government Printing Office, 2013). Regulations for medical devices are documented in Title 21 of the CFR and most of device regulations are included in 21 CFR Part 800 - 1299 (cf. Thomson Reuters

IDRAC [2], 2013). CFR regulations are binding until they are revised or withdrawn.

2.3 Other important documents

2.3.1 Other important documents – Germany

Besides the already mentioned legal documents, there are other *not* legally binding documents which are important to manufacturers of medical devices. The following represents them in their documentation hierarchy:

- *Guidance to Medical devices (MEDDEV documents)*
- *Harmonized Standards*
- *Medical Device Notified Body Recommendations*
- *Industry Standards*
- *Internal Standards*

For more detailed information please refer to **Appendix B.**

2.3.2 Other important documents – The USA

Besides the already mentioned federal laws of the FD&C Act and CFR regulations other regulatory documents are important to manufacturers of medical devices. The following list represents them:

- *FDA Guidance documents*
- *Congressional Committee Reports and Regulation Preambles*
- *FDA recognized consensus standards*
- *Industry Standards*
- *Internal standards*

For more detailed information please refer to **Appendix C.**

2.4 The need for a Quality system

2.4.1 The Requirement of a Quality system in Germany

Per MDD Annexes II, V and VI medical device manufacturers are required to have been an approved Quality system[13] implemented. The key medical

[13] In this Thesis the terms Quality system, Quality assurance and Quality management system meaning the same

device Quality system standard is the DIN EN ISO 13485:2012, 'Medical devices - Quality management systems – Requirements for regulatory purposes'. The standard provides a process orientated model for a Quality management system and defines requirements for the quality assurance in design, development, production and installation. As described earlier, the use of harmonized standards like DIN EN ISO 13485:2012 is voluntary and other quality system standards could theoretically be used to demonstrate compliance. However, the fact that DIN EN ISO 13485:2012 is a harmonized standard makes it the de facto standard for medical device manufacturers due to (1) the reason of the presumption of conformity to the MDD and with the essential requirements, (2) consideration of additional efforts to prove that the device is in conformity with the MDD and correlates with the latest state of the art when using other technical solutions, and (3) the application of a harmonized standard is recommended in Article 5 of the MDD.

2.4.2 The Requirement of a Quality system in the USA

Unlike Germany, there is no voluntary standard in the USA that provides a model or defines requirements for a Quality management system. Instead, manufacturers of medical devices must follow the element orientated quality management in accordance with 21 CFR Part 820 also known as Good Manufacturing Practices (GMP) that was first authorized by FD&C Act section 520(f).

Having a Quality system established is a legally binding post market requirement to manufacturers of finished devices as defined in 21 CFR 820.3(l) who intend to sell their medical devices. With regard to medical devices, the GMP regulation requires procedures for designing, purchasing, manufacturing, packaging, labeling, stocking, installing and servicing.

Due to the huge number of different device types the GMP regulation does not specify any details on device manufacturing. Within the given legal framework, manufacturers have to decide on their responsibility which procedures they need to develop and to implement to manufacture devices according to the current state of the art and to fulfill the requirements of the Quality System Regulation. 21 CFR Part 862 to 892 exempts certain devices

from GMP requirements due to their classification as long as the devices are not displayed or bear labeling as sterile (cf. Food and Drug Administration [1], 2013). However, even those devices manufacturers must keep complaint files as per 21 CFR 820.198 and records as per 21 CFR 820.180 (cf. Food and Drug Administration [1], 2013). Design control in accordance with 21 CFR 820.30 is the only element of the Quality System Regulation that applies to devices under an IDE (cf. Food and Drug Administration [1], 2013).

3 The Medical Device Directive – Overview and contents

The COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices is one of the three main European Directives for medical devices and covers a broad range of medical devices. The MDD, based on the 'New Approach', came into force in July 1994. Important goals of the MDD are harmonization of medical device related rules (e.g., laws), elimination of trade barriers and protection of community safety (cf. European Parliament and Council, 1993). With introduction of the MDD, a patchwork of local statutory provisions was replaced by a single unified system. Within this unified system, requirements for medical devices are specified that must be met prior to place medical devices on the market in the EU. Therefore, manufacturers must demonstrate compliance with the Medical Device Directive. After compliance is demonstrated, devices are accepted at the same time across all member states of the European Union and members of the EEA. Also in achievement regulatory approval in other countries like Australia or the USA compliance with the MDD is helpful. The MDD allows manufacturers the option of selecting from a number of different conformity assessment procedures. Compliance with the MDD is indicated through affixing the CE-Mark on the device after a conformity assessment was performed successfully. Since June 1998 all medical devices which are marketed within the EU must bear the CE marking.

Under the COUNCIL DIRECTIVE 93/42/EEC in Article 1 no. 2a medical devices are defined in as:

“any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

- *diagnosis, prevention, monitoring, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,*
- *investigation, replacement or modification of the anatomy or of a physiological process,*
- *control of conception,*

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;"

Under the COUNCIL DIRECTIVE 93/42/EEC in Article 1 no. 2b an accessory is defined as follows:

"'accessory' means an article which whilst not being a device is intended specifically by its manufacturer to be used together with a device to enable it to be used in accordance with the use of the device intended by the manufacturer of the device;"

The MDD consists of three sections:

1. An Introduction section which creates the legal basis for the Articles and Annexes, the "Whereas" section.
2. The Article section defines 23 Articles. Medical device manufacturers have to meet the requirements defined in the Article section if they intend to market their device within the EU and to be in compliance with the MDD. Thus it is necessary to incorporate the MDD requirements into the Manufacturers Quality system.
3. The Annex section contains Annexes I-XII.

For more information to the Annex section please refer to **Appendix D.**

The Annex I of the MDD is the most critical of the Annexes as it details the essential requirements for a medical device. The relevant essential requirements must be met to demonstrate the safety and effectiveness of the device.

The last MDD amendment 2007/47/EC entered into force on national level on March 03, 2010. Please refer to **Appendix E** for information on the most significant changes to COUNCIL DIRECTIVE 93/42/EEC by 2007/47/EC.

4 21 CFR Part xxx – Overview and contents

Medical devices are defined in FD&C Act section 201(h) as follows:

"The term "device" (except when used in paragraph (n) of this section and in sections 301(i), 403(f), 502(c), and 602(c)) means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is —

(1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them,

(2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or

(3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

The Federal Food, Drug, and Cosmetic Act (FD&C Act) is federal law and the basic regulation for medical devices. The FD&C Act establishes the power of the Food and Drug Administration (FDA) agency in relation to the supervision over medical devices. The FD&C Act is enforced by the Code of Federal Regulations (CFR). The CFR contains a collection of all federal agency regulations with the purpose of providing official regulations unified in one complete and organized system that is being updated by the Federal Register[14] (cf. National Archives, 2013). To make sure the latest version of any agency regulation or rule is used publications from both, the CFR and the Federal Register, must be used in combination (cf. National Archives, 2013). The legally binding CFR rules and regulations, also named administrative law, govern for the most of medical devices questions to design, clinical evaluation, manufacturing, packaging, labeling, and post market surveillance within the 21 CFR Part 800 - 1299 (cf. Thomson Reuters IDRAC [2], 2013).

[14] Federal Register is the official journal of the federal government. https://www.federalregister.gov/policy/about-us

As noted above FD&C law is enforced by the Code of Federal Regulations (CFR).

The basic unit of the CFR consists of:

1. Title
    1.1. Chapters
        1.1.1. Parts
            1.1.1.1. Sections

The main portion of medical device is regulated by FDA in 21 CFR Part 800 - 1299 (cf. Thomson Reuters IDRAC [2], 2013). In context with the present master thesis the most significant CFR parts are presented in **Appendix F**.

5 Device Classification System

5.1 The Device Classification System in Germany

According to Article 9 of the MDD medical devices must be classified. The device classification is the responsibility of the manufacturer. The principle of the classification rules is the risk potential of the medical device to harm the human body. Therefore, the classification system is predicated on the risk in relation to the devices´ technical design and manufacturing (cf. European Parliament and Council, 1993). The purpose of device classification is to determine the potential conformity assessment processes that are available (cf. EUROPEAN COMMISSION, 2010) as the conformity assessment processes depend on the risk of the device.

The Annex IX of the MDD provides eighteen rules for classification determination of medical devices and accessories. Furthermore the MEDDEV 2.4/1 'Classification of medical devices' Rev. 9, June 2010 provides properly guidance on classification.

Within the MDD are four classes of device defined:

1. Class I for devices with the lowest risk
    - ❖ Class I measuring and class I sterile
2. Class IIa
3. Class IIb
4. Class III for high risk devices.

The basic considerations on which the classification system depends are the duration of body contact, the invasiveness of the device, the clinical site of use, if the medical device works with power supply and other considerations. In case of a disagreement regarding the foreseen device classification between the chosen Notified Body and the Manufacturer, the responsible competent authority, to which the Notified Body is allocated, determines the device classification (cf. European Parliament and Council, 1993).

At the end of the Chapter 5.2 *Table 1* provides an overview and comparison of the German medical device classification system versus those of the USA.

For more information on the German medical device classification system please refer to **Appendix G.**

5.2 The Device Classification System in the USA

The classification of medical devices is conducted by 16 advisory / device panels[15] in accordance with FD&C Act section 513 and is largely based on preamendment devices. The panels are defined in detail in 21 CFR Parts 862 to 892 (cf. Food and Drug Administration [4], 2012). Within these 16 advisory panels, more than 1.700 generic types of medical devices[16] are described and each one classified into one of three classes of medical devices. The classification scheme of devices is both, risk-based (FD&C Act section 513(a)(2)) and knowledge-based (preamendment devices). The intended use of the device and the indication for use are important parameters to evaluate the risk that the device poses to human health and to define each device class. Moreover, the classification of a device also depends on the degree of regulatory control needed to afford a reasonable assurance of a device´s safety and effectiveness. The device class influences applicable regulatory requirements with regard to its market clearance/approval because the higher the device class, the higher the necessary level of control is to ensure reasonable assurance of a device's safety and effectiveness and the more stringent the regulations. To ensure an appropriate level of control, the mechanisms of general controls apply to each regulatory device class[17] (e.g., Class I, II, and III). As the device risk increases in each class, moderate to high risk devices of Class II are in addition to the general controls, subject to special controls. As the mechanisms of the special controls are insufficient for high risk devices of Class III, a PMA is required instead of the special controls. For more detailed information about general and special controls please refer to **Appendix H.**

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[15] All devices legally marketed before May 28, 1976 got categorized through FDA into panels of generic device types (cf. Food and Drug Administration [4], 2012)

[16] 21 CFR 860.3(i) Generic type of device means a grouping of devices that do not differ significantly in purpose, design, materials, energy source, function, or any other feature related to safety and effectiveness, and for which similar regulatory controls are sufficient to provide reasonable assurance of safety and effectiveness.

[17] Special and general controls are defined in FD&C Act section 513. For more information on general and special controls please refer to **Appendix H.**

At the end of this Chapter *Table 1* provides an overview and comparison of the German medical device classification system versus those of the USA. The three classes of device as defined in 21 CFR Part 860 section 860.3 are described in more detail in **Appendix I**.

In most instances a device can be classified by finding the applicable device description in 21 CFR Part 862-892 via advisory/device panels, or through the use of FDA´s classification database. If no classification is available due to a lack of matching results with any of the 16 advisory panels or non-availability of a preamendment device, the questioned device is, in the majority of cases a "first-of-a-kind-device" (cf. Food and Drug Administration [3], 2012) and is automatically classified as Class III in accordance with FD&C Act section 513(f)(1). This implies that the device is subject to the PMA procedure.

5.2.1 Reclassification and the De Novo process

Based on the FD&C Act[18] the FDA implements the reclassification requirement through 21 CFR Part 860 subpart C. The FDA may reclassify a preamendment device on its own to adjust the classification according to the latest knowledge or due to an outside petition in accordance with FD&C Act 513(f)(3) (e. g., from a manufacturer), that was submitted to FDA. In order to become accepted in a petition reclassifying a device, the manufacturer must demonstrate that the devices´ safety and effectiveness can adequately be ensured in a lower device class. Through the FDA´s 515 program (cf. Food and Drug Administration [4], 2013) the FDA reclassifies preamendment Class III devices into Class II or Class I with the consequence that no PMA but a premarket notification has to be submitted. For more information on the 515 program please refer to **Appendix J.**

For novel types of medical devices that pose only low to moderate risk but were classified in Class III due to the lack of substantial equivalence to any legally marketed predicate device, manufacturers may find in FD&C Act section 513(f)(2) an option to down-classify a device to Class II or Class I and thereby create an alternative route to market their devices. This rule is also

[18] FD&C Act sections 513, 514(b), 515(b), 520(l)

known as the De Novo process, it regulates the evaluation of automatic Class III designation on the basis of established risk-based classification criteria (cf. Food and Drug Administration [5], 2012).

A recently revised FDA guidance document “Draft Guidance for Industry and Food and Drug Administration Staff De Novo Classification Process (Evaluation of Automatic Class III Designation)” is available for download on the FDA homepage and provides further information on the de Novo process. The DRAFT guidance was issued on October 3, 2011 and is currently under annotation.

Table 1: Overview and comparison of the German medical device classification system versus those of the USA

Item	**Germany**	**USA**
Classification consequence	Classification decides over conformity assessment processes	Classification decides over premarket review process
Class	Class I, I(m,s)*, IIa, IIb, III *(m,s) device with measuring function or sterile device	Class I, II, III
Basis of the Classification system	Risk based’ system based on the risk potential of the medical device to harm the human body. Classification is predicated on the risk in relation to the devices´ technical design and manufacturing.	Risk-based scheme Knowledge-based scheme (preamendment devices) Classification parameters: Intended use and the indications for use are important parameter
Class I	Low risk device Self-certification of the device No device certification through a notified body Compliance with all MDD requirements CE marking of the device Conformity assessment per Annex VII	Low risk device General controls are adequate to ensure safety and effectiveness of the device Exempted from premarket review Limitations to GMP regulations

Item	Germany	USA
Class I m or s	Low risk device with sterile and / or measuring function Sterile / measuring function of the device requires certification through the Notified body Quality system certification Conformity assessment per Annex VII and II (without section 4) or Annex VII and IV, VII and V or VII and VI CE marking of the device inclusive the Notified body identification	Not Applicable
Class II	Not Applicable	Moderate to high risk device Premarket Notification (510(k)) (or in some cases PMA) required Clinical trial data may be required Some devices exempted from regulatory review process General and special controls are needed to ensure safety and effectiveness of the device
Class IIa	Higher risk device The Notified Body is required to certify the device or device group and the Quality system Conformity assessment per Annex VII and II (without section 4) or Annex VII and IV or Annex VII and V or Annex VII and VI CE marking of the device inclusive the Notified body identification	Not Applicable

Item	**Germany**	**USA**
Class IIb	Higher risk device Clinical trial performance were no adequate data exist The Notified Body is required to certify the device or device group and the Quality system Conformity assessment per Annex II (without section 4) or Annex III and IV or Annex III and V or Annex III and VI CE marking of the device inclusive the Notified body identification	Not Applicable
Class III	High risk device Clinical trial performance were no adequate data exist Notified Body is required to certify the device (no device group) and the Quality system Conformity assessment per Annex II or Annex III and IV or Annex III and V CE marking of the device inclusive Notified body identification	High risk device General controls plus PMA Class III 510(k) devices Clinical trial data required
Reclassification / De Novo process	Not Applicable	FD&C Act section 513(f)(2) De Novo classification process available for devices that automatically were classified into Class III FD&C Act 513(f)(3) allows reclassification of devices by FDA or due to an external petition

6 How to place human medical devices on the market

6.1 How to market in Germany

6.1.1 The conformity assessment process and possible conformity assessment forms

As described above, a device must be evaluated through a conformity assessment prior to being placed on the market. For Class II and Class III device conformity assessments the involvement of a notified body is required. The technical documentation is object to the conformity assessment through the Notified Body for devices higher Class I (e.g., Class II). Thereby, the Notified Body randomly selects technical files[19] for review. In case of Class I devices, the technical documentation must be prepared by the device manufacturer and made available for review to the national competent authorities at any time. Please refer to **Appendix E** for data retention time information.

The technical documentation includes all information relating to and explaining the medical device as well as the design monitoring and design verification documentation of the device. Annex II Chapter 3.2c of the MDD describes the contents of the technical documentation. The list below shows some of the most important documents which are required by the MDD and must be included in the technical documentation:

- General device description
- Specifications and standards
- Risk management information
- Design validation and design verification information
- Pre-clinical and clinical data
- Labeling.

Annex II through VII defines various conformity assessment forms for medical devices that will be utilized by the designated Notified Body. The applicable conformity assessment form is chosen by the manufacturer and

[19] Technical file: contains the technical documentation for all class of devices except for class III. Design dossier contains the technical documentation for class III devices.

depends on the risk / class of the device. The higher the risk of a medical device, the more complex is the conformity process. **Appendix K** provides an overview of the possible conformity assessment processes. **Appendix L** provides a short overview of the contents of Annexes II to VII of the MDD.

The German Law on Medical Devices § 11 no.1 exempts in certain reasonable cases, (e.g., emergency situations, no alternative device available) medical devices from the requirement of the CE marking. In case of such exemptions, the responsible[20] competent federal authority (e.g., the BfArM or the PEI) approves the national distribution of devices which do not bear the CE marking for a restricted time frame. If necessary, the approval must be renewed to review the conditions which are required for the exemption application.

The total amount of time necessary to get a device on the market in Germany and the EEA via the CE-certification depends on the classification of the device. The manufacturer may place low risk devices (e.g., Class I) on the market immediately upon completion of the technical documentation. Medium risk devices (e.g., Class I Sterile, Class I Measuring and Class II) typically require about seven month from the completion of the technical documentation and first communication with the Notified Body (cf. Josh Makower, 2010). High risk devices (e.g., Class III) typically require a minimum of one year and often substantially longer to obtain marketing approval. The costs for the CE-certification through a conformity assessment process depends on many facts (e.g., company size, number of facilities, outsourced manufacturing processes) and is between 7000 Euro and 80 000 Euro (cf. Klaus-Dieter Ziel, 2011). Approximately 320 medical devices of Class III gaining marketing approval on the German market each year (cf. Dr. Tobias Weiler, 2013).

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20 The main competent federal authority for medical devices is the BfArM, the PEI (Paul Ehrlich Institute) is responsible for certain in-vitro diagnostics

6.2 How to market in the USA

6.2.1 Major options for marketing submission: The Premarket Notification process and the Premarket Approval process

6.2.1.1 The Premarket Notification procedure (510(k))

The Premarket Notification procedure, defined in 21 CRF Part 807 Subpart E, applies to all[21] devices intended for human use for those manufacturers gaining first access to US market except of devices which require a PMA or are exempt[22] from the 510(k) process. A premarket submission via 510(k) may also be applicable to repackagers and relabelers if the device labeling experienced a substantial change or if any device conditions are modified (cf. Food and Drug Administration [1], 2013). The FDA evaluates the 510(k) to determine if the device is substantially equivalent to a device that already is placed into one of the three classification categories. If the FDA finds that the 510(k) premarket submission demonstrates that the device is substantially equivalent to a legally marketed device, the FDA issues a device clearance which allows the marketing of the device.

To this, the applicant must prove that its device, with regard to safety and effectiveness, is “substantially equivalent” (cf. Food and Drug Administration [2], 2012) as defined in FD&C Act 513(i) to a legally marketed[23] medical device which is not subject to a PMA and which equates to the current state of the art. Such a legally marketed device is called as “predicate device” (cf. Food and Drug Administration [4], 2010) as defined in 21 CFR Part 807.92(a)(3). The manufacturer supplies evidence for the substantial equivalence by comparing its device to one or more predicate devices. Being substantially equivalent does not mean identical (cf. Food and Drug

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[21] 510(k) is required for (cf. Food and Drug Administration [4], 2010):
- First time marketing of devices which were not marketed by your company before 28.05.1976 (Medical Device Amendments to FD&C Act)
- Most changes in intended use of a device
- Changes or modifications to marketed devices that could have influence device safety and effectiveness

[22] Please refer to Chapter 6.2.2.1 Exemption from Premarket Notification of this Thesis

[23] Legally marketed in US as defined in: (21 U.S.C. §§ 360(n), 360c(f)(1) & 360c(i); 21 CFR 807.92(a)(3))

Administration [4], 2010); rather, it means that the key safety / efficacy features of the new devices are not worse than the predicate device.

Most of Class II devices, a few of Class I devices, and Class III devices for which a PMA does not apply[24], must run through the pre-market notification process (cf. Food and Drug Administration [4], 2010). In certain cases it may be required to conduct a clinical trial to gather necessary data to prove the safety and effectiveness of the questioned device. Prior to starting a clinical trial, the FDA must approve an Investigational Device Exemption (IDE). A list of 510(k) cleared medical devices for the previous month is available on the FDA homepage around the 5th of each month (cf. Food and Drug Administration [1], 2009).

Although the FDA regulations 21 CFR Part 807.81 allow 90 days to review and determine the substantial equivalence of a 510(k) device, on average, the amount of time from first filing a 510(k) until clearance is ten months (cf. Josh Makower, 2010). On average, the amount of time from first FDA communication (e.g., clinical trial conduction) until clearance is 31 month (cf. Josh Makower, 2010).

The standard review fee for a 510(k) is $4,960 and for small business $2,480 in 2013 (cf. Food and Drug Administration [6], 2012). In reality, the costs for a premarket notification are much higher. On average, firms spent $24 million[25] (cf. Josh Makower, 2010) on FDA related steps. 3091 devices have been found substantial equivalent and have been cleared through a premarket notification process (cf. Food and Drug Administration [2], 2013) in 2012. There are three types of a 510(k) submission:

1. Traditional 510(k)
2. Abbreviated 510(k)
3. Special 510(k)

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[24] PMA exception of “Class III 510(k)” Devices: Preamendment devices for which FDA has issued a proposed rule classifying these devices into class III; but the final rule has been not issued yet, or the final rule was issued, but the rule did not include a date by which manufacturers or applicants are required to submit a PMA. Due to that reason would these class III devices achieve market access via the Premarket Notification procedure (510(k)) as long as a call for PMAs or a reclassification is not finalized (cf. Marjorie Shulman, kein Datum) (FD&C Act section 515). Devices distributed in the US market after May 28, 1976 (postamendment devices) that can show substantially equivalence to preamendment Class III devices and for which no regulation calling for a PMA has been published in 21 CFR may require a 510(k) (cf. Food and Drug Administration [2], 2009)

[25] Average total cost from concept to clearance/approval

For more detailed information on the three types of a 510(k) please refer to **Appendix M.**

If the regulatory review results in the FDA not issuing a clearance letter due to missing substantial equivalence to a predicate device, the applicant has the following options (cf. Food and Drug Administration [4], 2010):

- Filing a revised 510(k) containing new data;
- Requesting down classification through the De Novo process;
- Submitting a petition to down classify the device; or
- Submitting a PMA.

A recently revised FDA guidance document “Draft Guidance for Industry and Food and Drug Administration Staff - The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]” provides further information to help the manufacturer understand the 510(k) process. The DRAFT guidance was issued on: December 27, 2011 and is currently under annotation. It is available for download on the FDA homepage.

6.2.1.2 The Premarket Approval procedure (PMA)

In accordance with FD&C Act section 515, a medical device must go through the PMA process when it is for any reason classified as Class III, the highest class of device. Besides the general and special controls that apply to Class I and Class II devices respectively, the high risk of Class III devices additionally requires the PMA process prior to obtaining marketing approval.

The PMA approval is based on “reasonable assurance” (cf. US Goverment USCODE, 2012) of the device´s safety and effectiveness for its intended use. Clinical data to demonstrate the safety and effectiveness of the device to support the PMA as well as to prove any device claims are generally generated within a clinical trial under an Investigational Device Exemption (IDE) in accordance with 21 CFR Part 812. Prior to the initiation of an IDE[26] trial it must be approved by FDA.

[26] Besides 21 CFR Part 812 are other important FDA regulations that rule the conduction of clinical trials: 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 54, 21 CFR Part 820 subpart C

It is not allowed to market the device prior to receiving the FDA´s PMA approval. Key factors in obtaining a PMA approval are valid clinical data as mentioned above and good analysis of scientifically well-founded data and information. The application of the PMA requirements varies between Class III preamendment devices[27], Class III postamendment devices[27] (cf. Food and Drug Administration [2], 2009), and Class III transitional devices[27]. The FD&C Act 515(d)(6) requires the submission of PMA supplements for any device modification that influences device´ safety and effectiveness. The 21 CFR Part 814.20 describes the elements that are required in a PMA application.

For Class III devices which require a PMA there are four different methods for gaining market access available (cf. Food and Drug Administration [7], 2012):

- Traditional PMA
- Modular PMA
- Streamlined PMA
- Product Development Protocol (PDP) PMA

For more detailed information on the above described PMA methods please refer to **Appendix N**.

The scientific and regulatory review by the FDA within the PMA process consists of three review steps and one final decision making and notification step as described below (cf. Food and Drug Administration, 2011):

- Filing PMA review according to 21 CFR 814.42; FDA staff reviews from an administrative point of view if the PMA is complete and able to be filed;
- In-depth review according to 21 CFR 814.44; FDA experts perform a fundamental review of the Quality system and the scientific and regulatory information included in PMA

[27] Postamendment device is a device that is marketed on or after May 28, 1976. Preamendment device is a device that was marketed before May 28, 1976. Transitional devices are devices that were regulated as drugs prior to the May 28, 1976. Any device that was approved via the New Drug Application (NDA) procedure is now subject to the PMA regulations.

- Optional depending on FDA decision: Panel review according to 21 CFR 814.44; Proper advisory committee performs the panel review and makes recommendations
- Notification of Approval or denial according to 21 CFR 814.44; after final consultation and documentation of decision making facts, FDA notifies applicant about approval or denial and informs the public via the internet

For more information on the PMA application process please also refer to **Appendix O**.

Although the FDA regulations 21 CFR Part 814.40 allow 180 days[28] to review and determine a PMA, on average, the amount of time starting from first communication (e.g., clinical trial conduction) with the FDA until PMA approval is 54 month (cf. Josh Makower, 2010). However, FDA deficiencies and the manufacturer´s replies will extend the approval timeline in some cases to 70 months (cf. Josh Makower, 2010).

There are four possible outcomes of the FDA review process (cf. Food and Drug Administration, 2011):

- Approval order (21 CFRE Part 814.44(d)),
- Approvable letter (21 CFR Part 814.44(e)),
- Not approvable letter (21 CFR Part 814.44(f)),
- Order denying approval (21 CFR Part 814.45),

For more detailed information on the outcomes of the FDA review process please refer to **Appendix P.**

As opposed to the Premarket Notification procedure, the PMA process includes a provision for a preapproval inspection by FDA personnel. Thereby, certain aspects of the Quality system as required per 21 CFR Part 820 with regard to the PMA device are inspected. In particular, designing, manufacturing and processing of the device is inspected to verify compliance with the PMA application. Post-approval inspections in which changes to the PMA approved device, to its environment or to the Quality system are

[28] The 180 day period starts after FDA receives a PMA that is accepted for filing and to which no major amendment is submitted.

typically assigned within eight to twelve months post-approval (cf. Food and Drug Administration [3], 2009).

The standard review fee for a Premarket application is $248,000 (cf. Josh Makower, 2010) and for small business $62,000 (cf. Josh Makower, 2010) in 2013. In reality, the costs for a PMA application process are much higher. According to a survey of over 200 medical device companies, companies spent $75 million[29] (cf. Josh Makower, 2010) in average on FDA related steps. In 2012 only 39 devices were approved through a PMA (cf. Food and Drug Administration [3], 2013).

A list of PMA approved and denied medical devices of the previous month, together with further information (e.g., the data which led to FDA decision (Summary of Safety and Effectiveness Data), is available on the FDA homepage around the 5th of each month (cf. Food and Drug Administration [4], 2009).

For information on the current FDA review procedures please refer to **Appendix Q.**

6.2.2 Other options gaining marketing approval

6.2.2.1 Exemption from the Premarket Notification

Almost all Class I devices and some Class II devices (cf. Food and Drug Administration [8], 2012) may be exempted from the Premarket Notification process by regulation. The legal basis for the exemption of such devices is laid down in FD&C act 513(d)(2)(A). Besides the exclusion of preamendment[30] devices which have not been substantially changed or otherwise altered, 21 CFR Part section 807.85 defines further exceptional cases from the Premarket Notification (510(k)) requirement. Exempt status and any limitations on exemptions can be found in 21 CFR Parts 862-892.

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[29] Average total cost from concept to clearance/approval

[30] "For purposes of 510(k) decision-making, the term "preamendment device" refers to devices legally marketed in the U.S. by a firm before May 28, 1976 and which have not been significantly changed or modified since then; and for which a regulation requiring a PMA application has not been published by FDA (cf. Food and Drug Administration [8], 2012)

6.2.2.2 Humanitarian device exemption (HDE)

Medical devices with the purpose to treat or diagnose rare conditions or diseases concerning small patient populations and which fall under the Humanitarian Use Device (HUD) definition in 21 CFR 814.3(n) can, after the HUD application is designated, submit an HDE marketing application. Content and format of the HDE submission is similar to a PMA application; however, valid clinical trial results to prove effectiveness, safety and clinical performance of the HUD are not necessary to perform (cf. Food and Drug Administration [1], 2010). The HDE application must include data and information related to any risk that the device may pose to patient or user health. Furthermore, information that outlines risk versus benefit, evidence that there is no device of this type being legally marketed as well as evidence that marketing without a HDE would not be possible (cf. Food and Drug Administration [1], 2010) must be included in the HDE application. After obtaining HDE approval the device must include special labeling that identifies the device as HUD. Devices which are HDE approved are only allowed for use in clinical sites that have an Institutional Review Board (IRB) available (cf. Food and Drug Administration [1], 2010).

7 Certification process

7.1 The Certification process in Germany

To be allowed to distribute medical devices manufacturers must comply with the MDD and special German requirements for marketing. Prior to CE marking and distributing medical devices, the manufacturer must be certified by a notified body to show that the device is in compliance with the MDD. Only Class I devices are exempted from the CE certification through a notified body. The Notified Body certificate that is issued after successful certification has a validity of five years. During the certification audit the most important document that is reviewed is the technical file of a device (e.g., Class II device). Design dossiers of Class III devices are always reviewed off-site. Examples of the content of a technical file are provided in **Appendix R**. The technical file includes all information to prove compliance with the essential requirements. In addition to the review of the technical file / design dossier, the Quality system according to DIN EN ISO 13485 is audited[31] by the Notified Body. The certification of the Quality system is valid for three years but will be checked on an annual basis during the surveillance audits.

A typical Quality system according to DIN EN ISO 13485 includes procedures and work instructions to implement the MDD requirements. Moreover, the Quality system standard specific requirements must also be implemented. In **Appendix S** examples of procedures and contracts typically required by the MDD and examples of typically required DIN EN ISO 13485 procedures are provided.

7.2 The Certification process in the USA

To be allowed to distribute medical devices in the US, manufacturers must have a device that is 510(k) cleared, PMA / HDE approved or exempted. The Premarket Notification and the Premarket Approval / HDE processes are regulatory review procedures performed by the FDA. There is no procedure comparable with the certification process in Germany / EEA, and the FDA

[31] Audit: Formal examination performed by a notified body with the purpose to review if predetermined requirements are met.

does not issue a certificate like the EC certificate that shows compliance with the applicable CFR regulations or FD&C Act sections.

However, beside the demonstration of the safety and effectiveness of the device, is the compliance with the GMP requirements in accordance with 21 CFR Part 820 (Quality System Regulation (QSR), known as the GMP requirements) an important part of the clearance / approval. Even exempt devices must consider general GMP requirements (e.g., concerning records (820.180) and complaint files (820.198)). Manufacturers must implement a Quality system that meets the requirements as defined in the QSR. The 21 CFR Part 820 is a regulation issued by the FDA and regulates processes that may influence the safety and effectiveness of medical devices. Mainly, these are processes like design, manufacturing, packaging, labeling, storage and delivery of medical devices. The QSR is considered as federal law. Quite a few procedures and work instructions are necessary in order to implement the GMP requirements. The FDA will inspect facilities to determine if the applicable GMP regulation requirements are implemented appropriately and may issue a certificate of GMP compliance of a manufacturer to allow easy export to foreign countries.

In **Appendix T** are samples of typically required GMP procedures provided.

8 Other national requirements

8.1 Pre- and Post -marketing requirements for Germany and the USA

In addition to the MDD requirements, Germany has some special pre – and post marketing requirements to consider. The pre- and post -marketing requirements required by the FDA are similar to the German requirements. The most relevant pre- and post -marketing requirements for medical devices are provided in *Table 2* below. For more detailed information on pre- and post -marketing requirements for medical devices please refer to **Appendix U.**

Table 2: Pre- and post -marketing requirements in Germany and in the USA

Pre-marketing requirements	
Germany	**USA**
Labeling (§11 no. 2 and §5 of the German Law on Medical Devices (MPG))	Labeling (21 CFR Part 801)
Notification obligation (§25 of the German Law on Medical Devices)	Establishment registration and device listing (21 CFR Part 807)
Clinical trial requirements (§§19 to 24 of the German Law on Medical Devices)	Investigational device exemption (21 CFR Part 812)
Safety officer (§30 of the German Law on Medical Devices)	Premarket notification as per 21 CFR Part 807 Subpart E
Medical device consultant (§31 of the German Law on Medical Devices)	Premarket Approval (21 CFR Part 814)
Prescription status (Decree concerning the Availability on Prescription only of Medical Devices (MPVerschrV))	Quality System Regulation (QSR) / Good manufacturing practices (GMP) (21 CFR Part 820)
Registration requirement (Electrical and Electronic Equipment Law (ElektroG))	
Registration requirement (Electrical and Electronic Equipment Law (ElektroG))	
Decree on Distribution Channels for Medical Devices (MPVertrV)	

Post-marketing requirements	
Germany	**USA**
Medical device vigilance (MPG and MPSV)	Medical device reporting (21 CFR Part 803)
Pricing and reimbursement of medical devices (Social Code V (SGB V))	Reports on recalls, corrections and removals (21 CFR Part 806, 21 CFR Part 810 and 21 CFR Part 7)
Advertising and promotion of medical devices (Law on Advertising in the Field of Healthcare (HWG))	Post-market surveillance studies for certain class II / class III devices (21 CFR Part 822)
Notified body surveillance and recertification audits (MDD)	Medical device tracking (21 CFR Part 821)
	Quality system regulation (QSR) / Good manufacturing practices (GMP) (21 CFR Part 820)
	GMP inspections by FDA personnel or accredited persons
	Annual reports (21 CFR Part 814.84)
	PMA approved devices:
	Adverse reaction and device defect reporting (21 CFR Part 814.82(a)(9))
	PMA supplement (21 CFR Part 814.39)
	Post-approval studies
	Post-approval inspection

9 In summary: General considerations

The **Appendix V** summarizes items for Germany and the USA which should be considered when it is desired for a medical device gaining market access to the German / European or the US market.

Furthermore, *Table 3* below outlines the differences between the German regulatory system and the regulatory system of the USA.

Table 3: Differences between the German regulatory system versus those of the USA

Item	Germany	USA
Regulation	MDD to be transformed into national law, deviations from the MDD allowed	Implementation of the US Law (FD&C Act) by legally binding FDA regulations, enforcing of FD&C Act, no deviations allowed which soften the FD&C Act
Classification	In first instance the manufacturer has to decide over classification, MEDDEV guidance is provided, Manufacturer has to choose one of the applicable conformity assessment, depending on class of device Class I, I sterile, I measuring, Class IIa / IIb and Class III Device safety proven by evaluated clinical data Differences between manufacturer and the Notified Body with regard to the classification are decided from competent authority	21 CFR regulations define the device class and under which regulatory review process (e.g., 510(k) or PMA) the device is gaining market access Class I, II, III Intended use and Indication for use De Novo process or a manufacturer petition requesting a reclassification may be available

Item	Germany	USA
Quality system	It is up to the manufacturer if a harmonized quality standard (e.g., DIN EN ISO 13485) to implement the required Quality system is used Quality system is required in most cases (not for Class I only devices) Process orientated system Inspection of Class III devices every two years, No predefined inspection frequency for Class I and Class II devices FDA inspections performed by the FDA or since 2006 through a third party	It is law that the manufacturer has to follow and implement the Quality System Regulation 21 CFR Part 820 (GMP requirements) A full or partly Quality system is always required Element orientated system EC-certification audits every five years, DIN EN ISO 13485 surveillance audits annually and recertification audits every three years The Notified Body performs the Quality system and MDD certification audits, responsible Länder authority may inspect manufacturing facilities as well
Clinical evaluation	Proof of device safety and performance as well as demonstration of the low device risk, pre-clinical data (e.g., biological safety of the device (Biocompatibility testing, Bioburden testing))	Proof of safety, efficacy and patient benefits, Post market surveillance studies may be necessary
Marketing process	Conformity assessment by Notified Body to certify compliance with the MDD requirements and the Quality management system (e.g., according to DIN EN ISO 13485), CE marking	Premarket Approval (PMA) or Premarket Notification (510(k)), Approval letter or Clearance letter
Review approach for the device approval	Top- Down	Bottom-Up
Basis of the device approval or clearance	Certification is based on fulfillment of essential requirements acc. MDD; Harmonized standards covering MDD requirements	Clearance is based on the Substantial equivalence (510(k)) Approval is based on the reasonable assurance (PMA) of the device
Where are the device specific requirements defined?	21 CFR Parts 800 - 1299	Essential Requirements as defined in Annex I of the MDD

Item	Germany	USA
Renewal of the Approval	Every five years (EC Certificate)	No renewal required but annual reports for the device are mandatory
Responsibility	Responsibility and performance of conformity assessment procedures delegated from competent authority to the Notified Body -Decentralized approach	FDA is responsible for performing the premarket review and all other device related actions (e.g., device vigilance) - Centralized approach

10 Critical Examination

10.1 Regulatory framework

Due to the efforts of the European community to harmonize European regulations and standards in order to eliminate barriers to trade and to protect public safety, the main Medical Device Directives are based on the new and modular approach. The approaches lead to the manufacturers taking sole responsibility in respect to fulfillment of the essential device requirements as defined in the Directives. The approaches also lead to more freedom of choice for the manufacturer in determining the appropriate conformity assessment process as well as the use of international standards. Furthermore, CE-marked medical devices are allowed to be distributed throughout the EU without any trade barriers.

As already discussed are the most important requirements of the FDA regulations for medical devices included in the MDD as well. Not included in the MDD because of non-applicability are the following 21 CFR requirements:

- 510(k);
- PMA;
- IDE;
- HDE;
- De Novo process and reclassification;
- Registration and listing;
- Enforcement policy.

The MDD stipulates a decentralized approach. Review and approval of medical devices are delegated to the Notified Body. The Notified Body is responsible to perform the conformity assessment with the aim of the CE-certificate that shows compliance of a medical device with the legal requirements. This device approval system is very efficient as it shortens the approval timelines for all device classes and thus, patients and users have fast access to novel devices and technologies without cutting back on the safety of a device. Furthermore, the approval is better accomplishable as the requirements are less, especially in terms of clinical data requirements. According to §3 of the MPG, clinical data may be gathered from clinical trials,

from miscellaneous trials of similar devices or from clinical literature. The MPG does not require clinical trials specifically, even not for high risk Class III devices. In Germany, clinical trial data only support manufacturer information regarding safety and performance of the device. There are no requirements to prove the benefit of the device for the patients or users.

On the basis of the FD&C Act develops the FDA legally binding rules and regulations which further specify and detail the implementation of the requirements of the FD&C Act. Unlike Germany, manufacturers do not have the freedom of choice in determining the appropriate review process for the approval, or in the use of international standards because legally binding rules and regulations define how devices to be brought to the US market. Moreover, manufacturer's efforts gaining marketing approval of a device are much higher. For low to medium risk devices manufacturers need to find one or more predicate or preamendment devices in order to demonstrate substantial equivalence in a premarket notification application. The premarket approval application for high risk devices requires the most efforts (e.g., financial aspects, processing time) because the manufacturer must prove reasonable assurance of the device safety and effectiveness. Cleared or approved medical devices can only be distributed within the US market.

The US laws assign the FDA to review and approve medical devices for marketing. The FDA is responsible for all medical device related actions (e.g., pre- and -post marketing actions) and their performances. This centralized model slows down the approval time of medical devices especially for novel devices that require a PMA, but also for certain low-medium-risk 510(k) devices that require clinical data. In contrast to Germany, clinical data must demonstrate the benefit of the device for the patients or users beside of their safety and efficacy. This is an advantage for patients and device users since no ineffective devices may enter the market in the US.

The approaches between both countries are completely different. However, the regulatory processes for marketing approval of devices of both countries are highly regulated and both regulatory systems are eligible to provide safe and effective devices to the public (cf. S. Davis, 2011).

10.2 Quality system

In Germany, the standard for a Quality management system for medical devices, the DIN EN ISO 13485 standard, is a voluntary but important tool for manufacturers to show compliance with the essential requirements of the MDD. The DIN EN ISO 13485 standard provides a process orientated model for a Quality management system. After the initial certification audit, the Notified Body reviews the compliance of the Quality system with the relevant ISO standard annually during surveillance audits. The results of any audits conducted by the Notified Body are confidential as long as the certificate is not withdrawn. Users and patients do not get informed about any issues (e.g., device related issues).

Unlike Germany, the element orientated Quality System Regulation (QSR) as defined in 21 CFR Part 820, is legally binding to each manufacturer of medical devices and more rigid than the DIN EN ISO 13485 standard. Although the US Quality regulation is similar to the DIN EN ISO 13485 standard in content, there are subtle differences that must be considered when a Quality system is introduced, for example:

- QSR does not require a Quality manual;
- QSR require Device Master Records, Design History Files, Quality system records;
- QSR has specific requirements regarding document control (communication of changes to documents).

Because the FDA is responsible for all medical device related actions, the FDA performs its own inspections to investigate compliance with the QSR requirements. Furthermore, the FDA comes with more competence than the Notified Body in Germany / EEA. This enables the FDA to stop the manufacturing of medical devices instantly. There is no predefined investigation frequency for Class I or Class II medical devices. Manufacturers of Class III medical devices will be inspected by the FDA every two years. In contrast to Germany, serious findings are promulgated. By doing so, users, patients and competitors are aware of important deficiencies.

On the one hand leads the approach of the Medical Device Directive to more freedom of choice for the manufacturer in determining the appropriate conformity assessment process as well as the use of international standards (e.g., DIN EN ISO 13485). In reality, the German and EEA market favors medical devices that are manufactured under a certified Quality management system in accordance with DIN EN ISO 13485 standard. Therefore, the implementation of a Quality system according to DIN EN ISO 13485 standard is highly recommended for manufacturers of medical devices although it is voluntary.

10.3 Device classification system

The classification system of medical devices is similar in both countries but not comparable. While in the USA medical devices are categorized in Class I, Class II and Class III devices includes the German system in addition to the device classes of the USA devices of Class I Sterile and Class I Measuring.

In the regulatory system of the USA the device class influences the applicability of regulatory requirements with regard to its market clearance or approval because the higher the device class, the higher the necessary level of control is to ensure reasonable assurance of a device's safety and effectiveness and the more stringent the regulations. For example, silicone breast implants are classified in Class III and require a PMA, including clinical trial data. Furthermore, the PMA process includes a provision for a preapproval inspection by FDA personnel.

The disadvantage of the US classification system is the use of preamendment devices to classify today’s medical devices in the 510(k) process. If a medical device of Class I or Class II is substantially equivalent to a preamendment device, it will be reviewed under the 510(k) process and no clinical trial need to be conducted since the device is grandfathered. However, performance and analysis of clinical trials conducted before 1976 may be different than today. The safety and effectiveness of substantially equivalent devices may not be comparable to devices that were commercially distributed before 1976. In Addition, manufacturing processes, materials,

auxiliaries, design, surgical techniques and scientific knowledge also may have changed in between.

According to the MDD, the device class influences the applicable forms of conformity assessment with regard to its market approval because the higher the device class the more information is required to certify a device. For example, silicone breast implants are classified as Class III devices and thus, they require conformity assessment forms as defined in Annex II (e.g., Annex II.3 and II.4), Annex III and IV, or Annex III and V. The most widely used Annex for the conformity assessment of Class III devices is Annex II because the German and EEA market favors medical devices that are manufactured under a certified Quality management system in accordance with DIN EN ISO 13485 standard. The basic considerations of the classification system depend on elements which may pose a potential risk to the human body. This classification scheme may be more confident than the US system, since it considers each individual device and the device risk related elements in relation to the patient health.

10.4 Options gaining marketing approval

The options of both countries gaining market access for medical devices are not similar or comparable. Even the approaches to review the approval documentation are different. However, Class III devices in both countries must go through the most stringent regulatory process / conformity assessment process to receive marketing approval. There are no processes like 510(k), HDE or reclassification processes available in Germany /EEA. Due to the German system, such processes (e.g., 510(k), HDE, Reclassification) are not required at all.

As mentioned above, various conformity assessment forms are available to certify a device for the German / EEA market. During a conformity assessment the Notified Body randomly selects manufacturing documents of a device (e.g., technical file or design dossier) and device related processes for review and reviews the compliance of the Quality management system with the requirements of the relevant quality standard (e.g., DIN EN ISO 13485). Thereby the Notified Body uses the top-down approach; this means

the Notified Body gets a picture of the overall system first, and then concretizes the review from top (e.g., overall appearance of the system) to down (e.g., appearance of certain subsystems and review of certain individual processes of a subsystem in detail). In order to meet predefined time frames the depth of review may be limited. Due to this approach the Notified Body does not review the complete system in all its details during an audit but rather selects different devices and processes and its related documentation on a randomly basis for review. By doing so, the Notified Body has covered most of the Quality system of a company after a number of audits. In addition to the Annex II.3 requirements, manufacturers of Class III devices must apply for a design examination of the device desired for CE marking and marketing approval by the Notified Body. Once a device manufacturer has fulfilled its notification obligation according to §25 of the Law on Medical Devices; on the basis of §26 of the Law on Medical Devices the competent Länder authority is allowed to inspect the manufacturing facilities and taking device patterns without prior notice at any time.

The Premarket Notification procedure and the Premarket Approval process are the basic types of device authorizations which allow a device to be fully marketed in the USA. Within the regulatory and scientific review processes either, the substantial equivalence, or the safety and effectiveness of a device is evaluated by the FDA Thereby, the FDA uses the bottom-up approach; this means the FDA begins the review with the extensive analysis of any details of provided base information / data. Then, the reviewed information and data are interconnected to the next higher level (e.g., documentation or information level) or subsystem. The review process ends with the complete system / highest level. Aim of this approach is to reproduce and understand every single detail of data and information which are provided. The bottom-up approach is very eligible to find errors and discrepancies in the submitted application documents. Certainly, the bottom-up approach is quite time consuming. A preapproval inspection performed by the FDA is part of the premarket application. During the inspection, the Quality system of the company is inspected to the accordance with the GMP regulations.

The regulatory systems for device approval are different. The top-down approach facilitates the review more quickly as the bottom-up approach; but both are eligible to provide safe devices with a comparable number of medical device recalls (cf. S. Davis, 2011).

However, the Poly Implant Prothèse (PIP) scandal (cf. BfArM, 2010) from 2010 raised questions about the device approval system in accordance to the MDD. Could the PIP scandal may also occur in the USA?

In both countries, Germany and the USA, silicone breast implants are classified into Class III. However, unlike the USA, the German law does not require clinical data gathered from clinical trials explicitly; but it requires beside of Annex II.3, in Annex II.4 the design examination of the device. Furthermore, the competent Länder authority is allowed to inspect the manufacturing facilities and taking device patterns without prior notice at any time. However, the MDD requirements alone should be strict enough to ensure the safety and performance of a Class III device (e.g., like silicone breast implants).

The Premarket Notification requires clinical trial data, schedules a premarket approval inspection by the FDA and requires the conduction of post market clinical studies if applicable. The review approach is from bottom to up; data and information are analyzed in very detail. These requirements are should be eligible to ensure the safety and effectiveness of a Class III device.

In the context of high risk devices are processes, the Premarket Approval and the conformity assessment, eligible to provide safe and effective and / or well performing Class III devices.

However, the Poly Implant Prothèse (PIP) scandal was caused by a lot of criminal energy of the responsible persons (e.g., manufacturer). Audited persons (e.g., manufacturer) may show any inspector (e.g., FDA inspector) or auditor (e.g., Notified Body) the wrong documentation when criminal intent exists. An FDA inspector is not going to find the issue any more than a

notified body auditor unless the FDA goes in with a purpose[32]. However, under normal conditions, neither the FDA personnel nor the Notified Body personnel can assume that someone is lying or cheating to them. An excellent tool of the German system is the inspection by the competent Länder authority because the inspection may be performed without any presumption at any time without prior notice; device patterns may be taken[33]. Such an inspection would have been able to uncover the scandal earlier.

Although the Premarket Approval is based on clinical trial data, any document can always be falsified at least for the use of any non-approved silicone material for breast implants. An advantage compared to Germany is the post market clinical trial requirement, if agreed as an approval requirement; however, this is also no absolute safety against fraud[34].

10.5 Pre- and post-market requirements

Germany possesses quite a few pre marketing requirements which manufacturers have to fulfill. Except for a few requirements (e.g., Medical device consultant) most of the German requirements are also included in a PMA or 510(k) application (e.g., prescription status, distribution of a device).

The USA possesses quite a few post marketing obligations which manufacturers have to fulfill. Many of them are not required in Germany (e.g., annual reports) but some of them should be required in Germany as well (e.g., post market surveillance studies for certain devices) to ensure the approved medical device is safe, effective and well performing.

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[32] If the FDA assumes there is a real problem (e.g., lots of explants with chemical analysis showing that the explants don't match medical grade silicone), then there is going to be a real inspection with FDA personnel going to the manufacturer, raw material supplier, etc. Samples will be pulled and checked versus documentation.

[33] Please note the FDA may also inspect facilities at any time without prior notice.

[34] Where there's a will, there's a way.

11 Conclusion

Medical device companies who gain marketing approval in the European Union / EEA must in compliance with the MDD requirements. In particular, for most companies' means this being certified by the Notified Body to a quality management system standard (e.g., DIN EN ISO 13485) and the MDD. Various conformity assessment forms are available to certify a device for the German / EEA market. The device certification to obtain market approval through a conformity assessment is very efficient as it shortens the approval timelines for all device classes without cutting back on the safety of a device[96]. Therefore, manufacturers are able to make any medical device available to patients and users more promptly and at a lower price than in the US market due to the regulatory processes for medical devices within the European Union. Moreover, firms can modify devices quicker than on the US market and devices can be distributed throughout the EEA. In addition, a certified Quality system and certified MDD compliance may help companies which aim regulatory approval in non- EEA countries. However, there is no legal requirement which requires clinical trial conduction. This allows that ineffective but expansive medical devices may enter the German and EEA market. With the establishment of the new legal framework, the requirements for medical devices (e.g., on clinical data) are going to be more stringent. A further challenge for device manufacturers is to fully comply with the MDD requirements since many companies fail compliance due to missing experience with the MDD or a lack of resources (e.g., human resources, financial resources). This may lead to non-compliance to the MDD and may result in disability or to a lag in distribution of devices.

The PMA process is a high regulated process for device approval which is able to ensure that PMA approved devices are safe and effective and provide a benefit to patients or users. Otherwise, the PMA process is a time-consuming (e.g., due to clinical trial conduction, FDA review time) and cost intensive (e.g., due to clinical trial conduction) process which causes, compared to other countries, device lags due to the delayed or denied availability of novel devices and technologies. Clinical trial data required by a

PMA do not necessarily lead to less device recalls (cf. S. Davis, 2011), but ensuring the effectiveness and benefit of a medical device. PMA approved devices can only be distributed throughout the USA. Local medical device manufacturers and originators may miss incentives to start a PMA and may leave the USA to relocate to more convenient countries which providing market access more quickly.

Compared to the PMA process allows the Premarket Notification procedure marketing approval within a shorter time, and it does cost less money. Otherwise, the Premarket Notification allows the market access only to devices which show substantial equivalence and denies market access to new concept devices and technologies. Thus innovative medical devices need to go through a PMA process. In addition, through the increasing FDA requirements (e.g., on clinical device data) to 510(k) applications, more devices may require a PMA submission. As already mentioned above, this may lead to relocation of medical device companies or originators.

Both systems, the German and the US, are high regulated and eligible to provide safe, effective or well performing medical devices. None of these systems is perfect and each has it strengthens and debilities.

In last consequence, due to the current US regulatory processes for device approval, the development of innovative medical device may slow down in the USA in future.

12 Outlook

12.1 Outlook for Germany / EEA

Prior to the occurrence of the recent outrageous events[35] the European commission already worked on a revision of the current legal framework for medical devices necessary because of (cf. EUROPEAN COMMISION, 2012):

- ❖ the vast development in science and technology over the last two decades,
- ❖ different ways of interpretation and implementation of the EU regulations within the member states of the European Union caused unequal conditions in the prevention of patients and public health and facilitates the development of trade barriers to the European single market,
- ❖ the need for better provisions on device traceability and the need for a higher level of transparency for patients, health-care professionals and other interested persons,

Thus, the European commission compiled an elementary revision of the current legal framework for medical devices. The outcome was the adoption of a bundle of regulatory proposals on 26 September 2012 that consists of two proposals[36] (cf. EUROPEAN COMMISION, 2012):

- "Proposal for a Regulation of the European Parliament and of the COUNCIL on medical devices, and amending DIRECTIVE 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009."
- "Proposal for a Regulation of the European Parliament and of the COUNCIL on *in vitro* diagnostic medical devices."

[35] Poly Implant Prothèse (PIP) scandal (cf. BfArM, 2010) and Rofil Medical Nederland B.V. breast implants silicone scandal (cf. BfArM, 2010) (occurred in 2010); the metal-on-metal hip implants issue (cf. MHRA, 2012) (occurred in 2012)

[36] For more details please refer to: Single market for goods **'New legislative framework' for marketing of products** http://ec.europa.eu/enterprise/policies/single-market-goods/internal-market-for-products/new-legislative-framework/; Last update: 05/02/2013

Within the commission proposal the items listed below were revised (cf. EUROPEAN COMMISION, 2012):

- Extension and clarification of the scope of the EU-law
- Notified Body shall be supervised in a more intensive way
- Strengthen the authority of the Notified Bodies (e.g., performance of unannounced audits)
- Detailed definition of rights and liability for manufacturers
- The Eudamed[37] database on medical devices shall be enlarged
- Tighten the rules on traceability of medical devices
- Tighten the rules for clinical investigations and increase the data requirements for clinical assessments
- Increased role of health and safety requirements
- Classification rules for in-vitro diagnostics similar to the MDD classification rules
- Establishment of a medical device coordination group

Assuming that the commission proposals will be adopted in 2014, they will become effective between 2015 and 2019 (cf. EUROPEAN COMMISION, 2012). Information on the ordinary legislative procedure that leads to the decision if the commission proposals become European law is provided in **Appendix W**.

To accomplish the necessities mentioned above, the European regulatory requirements for medical devices are going to be more though, reinforced and more transparent in future. The way medical devices achieve market access (via conformity assessment processes) shall remain since it is not the intention to implement a government procedure for regulatory review of device applications (cf. Dr. Tobias Weiler, 2013). However, Notified Body shall be subject to a more intensive supervision through competent authorities. Simultaneously, the Notified Body shall receive more competence in performing conformity assessments and audits. Furthermore, requirements on clinical data supply and data quality will increase. With the implementation

[37] EUDAMED - European Databank on Medical Devices. The Eudamed is an European database and an implementation of the medical device Directives requirements. Purpose of this database is to sustain market surveillance and transparency and to apply a homogeneous utilization of the Directives especially with regard to device registration requirements (cf. EUROPEAN COMMISSION, 2011).

of the new legislative framework into the national level, the German legislation will implement the reinforced requirements as well.

12.2 Outlook for the USA

From a global harmonization point of view, the FDA has made some steps forward and harmonized certain processes to speed the device application process and to comfort the conditions for the marketing access to US market. These steps are:

Third party review by FDA accredited persons

Third party reviewers that are accredited by FDA are allowed to perform the primary review of certain 510(k) devices of Class I or Class II that are listed by FDA[38]. The program is based on the Food and Drug Administration Modernization Act (FDAMA) of 1997 (cf. Food and Drug Administation [5], 2009). The third party reviewer then submits the review results together with a recommendation and the 510(k) application to FDA for final decision. The purpose of the third party review is to speed the 510(k) process to keep decision deadlines. Besides the advantage of a faster clearance, a further plus is that most of the third party reviewers have offices not only throughout the US but also internationally (e. g., in Germany). A local office eases and supports interactions and communications between reviewing third party and applicant.

Third party inspections by FDA accredited persons

Based on the FD&C Act Chapter VII section 704(g), the FDA accredits third parties to carry out GMP inspections of medical device manufacturers. However, the conditions are limited[39]. Moreover, only certain Class I or Class II manufacturers are eligible and allowed to request a third party inspection (cf. Food and Drug Administration [5], 2010). Like third party reviewers, most third party inspectors have offices internationally (e. g., in Germany). A local office eases and supports interactions and communications and offers flexibility.

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[38] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfThirdParty/current.cfm, 20.03.2013

[39] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/PostmarketRequirements/ThirdPartyInspection/ucm125410.htm, 20.03.2013

Pilot multi-purpose audit program between Canadian regulatory authority(CMDCAS) and FDA

In this program only one third party is necessary to inspect or audit a device manufacturers Quality system that meets both, Canadian and US quality system requirements. Within the program the effectivity of such single third party inspections is assessed (cf. Food and Drug Administration [5], 2010).

Summary Technical Document (STED) program

The STED program was implemented by FDA´s CDRH in 2003 (cf. Food and Drug Administration [6], 2010). The STED format was developed by the no longer existent Global Harmonization Task Force[40] (GHTF) (cf. Food and Drug Administration [6], 2010). STED is a harmonized format to submit medical device applications and is accepted by many regulatory authorities worldwide. However, only certain types of regulatory review procedures are eligible to participate on the STED program. These types are:

- Traditional 510(k);
- Abbreviated 510(k); and
- Certain types of PMA.

Applications for in vitro diagnostic devices, PDP´s and HDE´s are not be able for participation on the program (cf. Food and Drug Administration [6], 2010).

The FDA has been increasing their requirements on clinical data for medical devices[84]. In order to tighten the regulatory requirements, the FDA has changed their interpretation of the regulations (cf. Quinlan-Smith, 2013). This result in the requirement of additional clinical data gathered from valid clinical trials to supplement a 510(k) application and for higher requirements in regards to statistical requirements (cf. Quinlan-Smith, 2013). Furthermore, the FDA more strictly handles the indications for use statement and the categorization of a device (cf. Quinlan-Smith, 2013). This may lead to more devices that require a PMA submission.

[40] GHTF: voluntary group consisting of members from industry and national regulatory authorities from participating countries USA, Japan, Australia, Canada and EU. Purpose of the GHTF is to harmonize and standardize international regulation systems with regard to medical devices. Since October 2011 GHTF is replaced by International Medical Device Regulators Forum (IMDRF). http://www.imdrf.org/

Summary

Marlene Schulzensohn (May, 2013)

How to place human medical devices on the market?
An overview and critical examination of the regulatory requirements in Germany versus those in the United States

Manufacturers of medical devices need to know and follow specific legal and regulatory requirements if they want to place their devices on the German or United States market. Both, Germany and the USA, have their own distinct regulatory requirements that must be met prior to a manufacturer placing their medical device on the market.

Germany as participant of the European Union is subject to the European Economic Area (EEA) law. On the European Union level the Medical Device Directive (COUNCIL DIRECTIVE 93/42/EEC, known as MDD) of 14 June 1993 is the most essential of three core regulations. The DIRECTIVE 93/42/EEC covers a broad range of medical devices and defines requirements for marketing of medical devices. Important goals of the MDD are harmonization of medical device related laws, elimination of trade barriers and protection of community safety.

Except for certain exclusions, prior to a medical device being first placed on the market within the European Economic Area (EEA) which includes Germany it must bear the CE-Marking and, where required with reference to the conformity assessment, the identification number of the notified body. To receive CE-Marking the device must be assessed during a conformity assessment that depends on the class of the device.

The Federal Food, Drug, and Cosmetic Act (FD&C Act) is federal law and the basic regulation for medical devices. The FD&C Act establishes the power of the Food and Drug Administration (FDA) agency in relation to the supervision over medical devices. The FD&C Act is enforced by the Code of Federal Regulations (CFR). These legally binding rules and regulations, also named administrative law, regulate the most of the medical devices within the 21 CFR Part 800 - 1299.

Unlike in Germany, the USA market does not allow a conformity assessment through a notified body. Instead, a pre-market authorization is required prior to a medical device being first placed on the market in the USA. The pre-market authorization will be issued by the United States Food and Drug Administration (FDA), a regulatory authority in the USA. Basically there are two different types of device authorizations which allow a device to be fully marketed in the USA; the 510(k) Premarket Notification and the Premarket Approval (PMA).

The present master thesis provides a regulatory overview of the current ways on how to place a medical device on the German market and on the US market. The thesis also critically examines regulatory differences between both countries. Beginning with a short introduction of both country legal frameworks, the thesis then gives attention to the specific regulations. Important pre- and post-market requirements and other considerations will be addressed.

Pages: 58; Annexes: pages: 29

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cf. Food and Drug Administration, 2011. *http://www.fda.gov.* [Online]
Available at:
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Available at: http://www.wise-intern.org/journal/2012/documents/DeniseLiuWISEPresentationFinal.pdf
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Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/RadiologicalDevicesPanel/UCM300840.pdf
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Available at: https://www.zlg.de/servicenavi/aktuelles/meldung/article/aenderung-des-staatsvertrages-der-zlg.html
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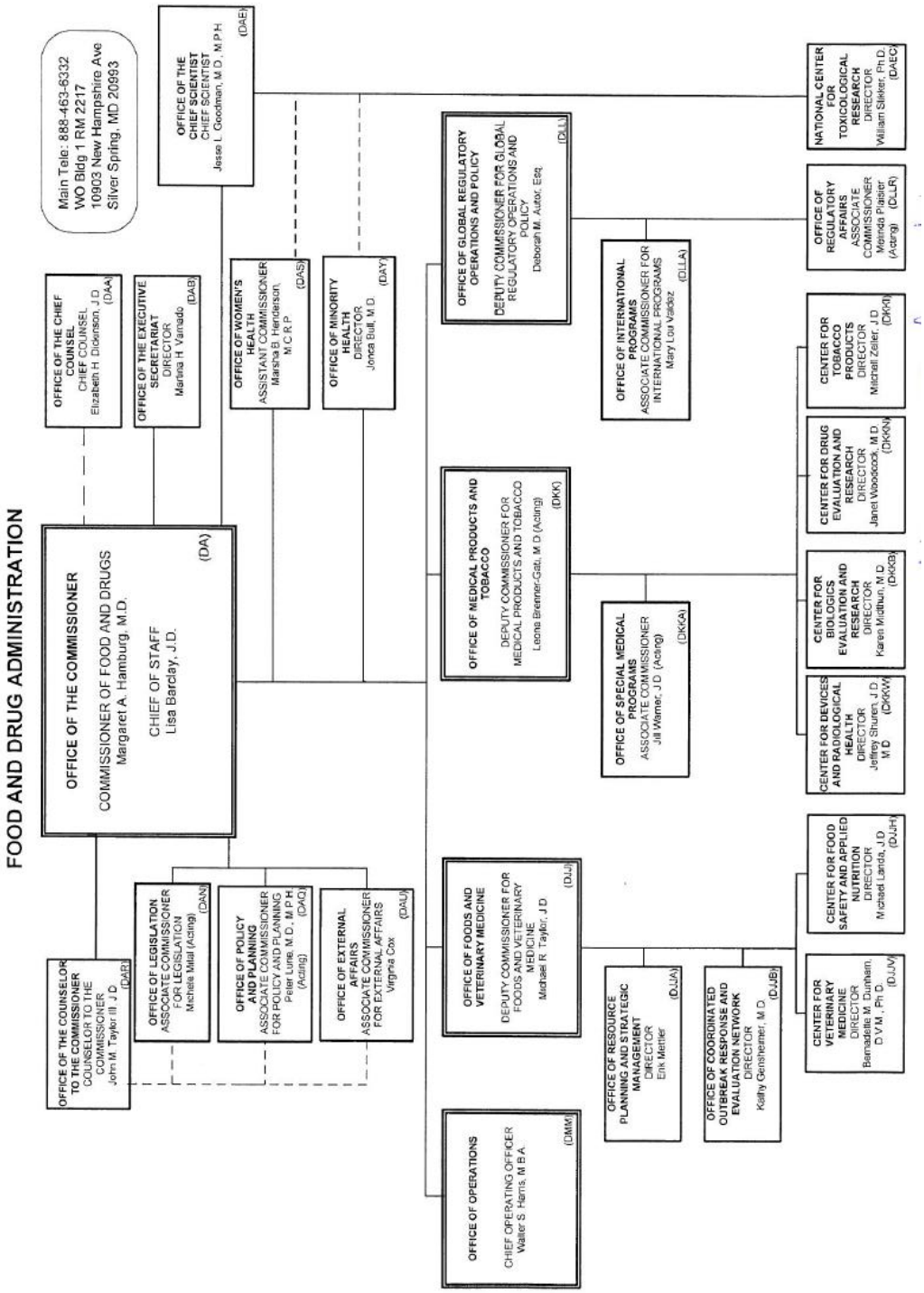
List of Appendices

Appendix A - FDA Organizational Chart (cf. Food and Drug Administration [9], 2012)



Appendix B - Other documents important for manufacturers in Germany

Not legally binding documents:

- *Guidance to Medical devices (MEDDEV documents)*
  Purpose of these guidance documents is to facilitate an overall approach by parties engaged in the conformity assessment procedures per MDD (cf. EUOPEAN COMMISSION [2], 2013).
  The MEDDEV documents include the inputs from several interested parties in the medical devices sector like Competent Authorities and/or Commission Services, Notified Bodies and industry (cf. EUOPEAN COMMISSION [2], 2013).
- *Harmonized Standards*
  These are European standards which were drafted from one of the three European Standard Organizations on request from the European Commission. Goal of a harmonized standard is to supply solutions for compliance with a legal provision. Medical device manufacturers or Notified Body can voluntary use harmonized standards to demonstrate compliance with legal EU provisions (cf. EUROPEAN COMMISSION [3], 2013). The references of harmonized standards will be published in the Official Journal of the European Union (OJEU).
- *Medical Device Notified Body Recommendations*
  These are guidance documents created by a group of Notified Bodies with the purpose to recommend solutions to technical issues came up during Notified Body meetings.
- *Industry Standards*
  Industry standards provide technical specifications and are devised by standardization organizations like ISO, ASTM, etc.
- *Internal Standards*
  These are manufacturer standards based on clinical needs of the device and are created when no harmonized or industry standard is provided.

Appendix C - Other documents important for manufacturers in the USA

Not legally binding documents:

- *FDA Guidance documents*
  FDA has issued a couple of hundred general and product specific guidance documents and published in Federal Register. Guidance documents reflect FDA´s current view on a regulatory matter. They are treated as recommendations and are not legally binding at all.
- *Congressional Committee Reports and Regulation Preambles*
  These documents indicate the intention of the Government and are not legally binding.
- *FDA recognized consensus standards*
  FDA has published a list of FDA recognized consensus standards on FDA Homepage. From FDA´s point of view supports the conformance with FDA recognized consensus standards the medical device review procedures e.g. IDE, HDE, PMA, PDPs, 510(k)) as it supports the determination of safety and effectiveness of medical devices. Although FDA recognized consensus standards are not legally binding the use of such standards is highly recommended in consideration of placing medical devices on the US market.
- *Industry Standards*
  Industry standards provide technical specifications and are devised by standardization organizations like ISO, ASTM, etc. In some circumstances e. g. when no FDA recognized consensus standards exists yet, Industry standards may be used.
- *Internal standards*
  These are manufacturer standards based on clinical needs of the device and are created when no harmonized or industry standard is provided.

Appendix D - Annexes of the COUNCIL DIRECTIVE 93/42/EEC (MDD)

- Annex I Essential Requirements which is subdivided into general requirements, requirements regarding Design and Construction which includes a risk analysis, an important element of the Essential Requirements.
- Annex II EC Declaration of Conformity (full quality assurance system)
- Annex III EC Type Examination
- Annex IV EC Verification
- Annex V EC Declaration of Conformity (production quality assurance)
- Annex VI EC Declaration of Conformity (product quality assurance)
- Annex VII EC Declaration of Conformity
- Annex VII Statement Concerning Devices for Special Purposes
- Annex IX Classification Criteria with Definitions, Implementing Rules and Classification
- Annex X Clinical Evaluation
- Annex XI Criteria to be met for the Designation of Notified Bodies
- Annex XII CE Marking of Conformity.

Appendix E - The most important changes to the COUNCIL DIRECTIVE 93/42/EEC as amended by 2007/47/EC (MDD)

- An intended medical purpose of the device is required
- Consideration of stand-alone software and software validation
- Software as a medical device when an intended medical purpose is defined
- Software with only generic function that is used in health institutions is not considered as medical device
- Integration of a single use device definition in Article 1
- Liberalization of the Confidentiality Chapter
- Data retention time (e.g. Technical documentation) is five years and 15 years for implantable devices
- Tightening of Clinical data, clinical data required for all class of devices
- Use of EUDOMED Database to pool data on devices under clinical investigation (not custom made devices)
- Incident reporting for custom-made devices
- Patients of custom-made devices shall receive information about the manufacturers name, address and random sampling by notified bodies
- For non EU manufacturers: a liability to appoint an authorized representative
- Changes to Annex IX may result in changes to the applicability of conformity assessment procedures
- Modifications in conformity assessment such as performance of design examination for representative devices or device groups
- Changes to Annex I may result in a new assessment of devices already bearing the CE marking
- Demands on the technical documentation increased
- Consideration of overlapping Directives such Directive 89/686/EC about personal protective equipment or Machinery Directive 2006/42/EC, if applicable

Appendix F - The most significant CFR parts in relation to this master thesis

- MEDICAL DEVICE REPORTING;
- MEDICAL DEVICES; REPORTS OF CORRECTIONS AND REMOVALS;
- ESTABLISHMENT REGISTRATION AND DEVICE LISTING FOR MANUFACTURERS AND INITIAL IMPORTERS OF DEVICES;
- ENFORCEMENT POLICY;
- MEDICAL DEVICE RECALL AUTHORITY;
- INVESTIGATIONAL DEVICE EXEMPTIONS;
- PREMARKET APPROVAL OF MEDICAL DEVICES;
- QUALITY SYSTEM REGULATION;
- MEDICAL DEVICE TRACKING REQUIREMENTS;
- MEDICAL DEVICE CLASSIFICATION PROCEDURES;
- LABELING and
- Exempt Devices.

Appendix G - Detailed information on the classification system of medical devices in Germany

Class I medical device:

Only minimal control is foreseen by the MDD for the lowest risk devices of Class I. MDD states in Article 11 that manufacturers of Class I devices must self-certify their devices. To self-certify a device, the manufacturer must prepare the technical documentation demonstrating compliance to the essential requirements and issue a declaration of conformity. Thus, neither a device certification through a notified body nor a certified Quality system is required. However, the manufacturer must comply with all MDD requirements and the devices must be marked with a “CE” to show compliance.

Class I sterile medical device / Class I measuring medical device:

For Class I devices that are sterile or have a measuring function, merely the sterile and / or measuring function requires certification through the Notified Body. The most typical conformity form to achieve certification of Class I sterile and Class I Measuring devices is via Annex V of the MDD. Other conformity forms are possible (Please refer to Appendix K). All aspects other than the sterility and measuring function of these devices are self-certified by the manufacturer like non-sterile / non-measuring Class I devices. As opposed to Class I devices, a notified body must issue a device certificate that covers the device or device group prior to CE marking the devices. The devices must be marked with a CE + Notified Body identification number to show compliance with the MDD. Furthermore, a certified Quality system (e.g. according to DIN EN ISO 13485) is necessary.

Class IIa and Class IIb medical device:

All aspects of the higher risk devices in Class IIa and Class IIb must be certified by the Notified body. A certificate issued from the Notified Body covers the device or the device group after the conformity assessment, typically via Annex II.3 of the MDD, was successful. The devices must be marked with a CE + Notified Body identification number to show compliance with the MDD. A certified Quality system (e.g., according to DIN EN ISO 13485) is necessary. Clinical performance of implantable Class IIb devices has to be proven on the basis of clinical trials where no adequate clinical data exist (cf. EUROPEAN COMMISSION, 2010).

Class III medical device:

The highest risk devices are Class III devices. Prior to placing a Class III device on the market, the MDD requires an explicit approval with respect to the conformity of the device. A certificate issued from the Notified Body covers only the questioned device after the conformity assessment, typically via Annex II.3 and Annex II.4 of the MDD, was successful. The devices must be marked with a CE + Notified body identification number to show compliance with the MDD. A certified Quality system (e.g., according to DIN EN ISO 13485) is necessary. Where no adequate clinical data exists, the clinical performance of implantable Class III devices has to be proven on the basis of clinical trials (cf. EUROPEAN COMMISSION, 2010).

Annex H - Samples for general and special controls

Class I, II and II devices are subject to *general controls* like (cf. Food and Drug Administration [10], 2012):

- Establishment registration and Medical device listing (21 CFR Part 807, FD&C Act section 510)
- Manufacturing of devices in compliance (21 CFR Part 820, FD&C Act section 520f)
- Device labeling requirements in accordance (21 CFR Part 801) (Part 809 In-vitro devices)
- Premarket Notification requirement if applicable (FD&C Act section 510(k))
- Banned devices (FD&C Act section 516)
- Prohibition against adulteration and misbranding (FD&C Act section 501, FD&C Act section 502)
- Keeping records and reports (FD&C Act section 519)
- Repair, notification, replacement, refund (FD&C Act section 518)
- Restricted devices (FD&C Act section 520e)

Class II devices are subject to *special controls* like (cf. Food and Drug Administration [10], 2012):

- Special labeling requirements
- Post market surveillance
- Patient registries development
- Mandatory performance standards
- Development and dissemination of guidelines
- Recommendations and other adequate actions
- Medical device tracking

Appendix I - Detailed information on the classification system of medical devices in the USA

Class I devices only pose a low risk to human health so that general controls are sufficient to assure safety and effectiveness. They are generally exempt from premarket review requirement / FDA clearance since any combination of general controls is sufficient to present reasonable assurance of the safety and effectiveness of devices. However, the exempt status and any GMP limitations should always be verified with 21 CFR Part 862-892.

Class II devices bear higher risk to human health. Here, general controls alone are insufficient to ensure reasonable assurance of a device´s safety and effectiveness. Therefore in addition to general controls, special controls are needed. Class II devices generally require the Premarket Notification (510(k)) prior to distribution in US. However, certain class II devices FDA listed and annotated as "(II)" are exempt from the Premarket Notification requirements of the FDAMA of 1997 but not from 21 CFR Part 820 requirements (cf. Food and Drug Administration [5], 2013).

Class III devices are used for supporting/sustaining human life or in preventing impairment to human health and they can bear an unreasonable risk of illness or injury e.g. new questions of safety and effectiveness due to novel technologies. Class III devices pose the highest risk to human health. Therefore, general or special controls are deemed insufficient to ensure reasonable assurance of device´ safety and effectiveness. Therefore, Class III devices generally require Premarket Approval (PMA) prior to distribution in US. Below provided is a summary of the information described above.

Overview device class and market submission option

Class of device	**How to market/ market submission option**
Class I exempt	510(k) exempted, verify with 21 CFR Parts 862 to 892 for any limitations on exemptions
Class II exempt	510(k) exempted, verify with 21 CFR Parts 862 to 892 for any limitations on exemptions
Class I non exempt	Premarket Notification (510(k))
Class II non exempt	Premarket Notification (510(k))
Class III	Premarket Notification (510(k))[41]
Class III	Premarket Approval (PMA)

[41] PMA exception of “Class III 510(k)” Devices: Preamendment devices for which FDA has issued a proposed rule classifying these devices into class III; but the final rule has been not issued yet, or the final rule was issued, but the rule did not include a date by which manufacturers or applicants are required to submit a PMA. Due to that reason would these class III devices achieve market access via the Premarket Notification process (510(k)) as long as a call for PMAs or a reclassification is not finalized[51] (FD&C Act section 515). Devices distributed in the US market after May 28, 1976 (postamendment devices) that can show substantially equivalence to preamendment Class III devices and for which no regulation calling for a PMA has been published in 21 CFR may require a 510(k) (cf. Food and Drug Administration [10], 2012).

Appendix J - The 515 program (cf. Food and Drug Administration [4], 2013)

The FDA must do five things to finalize the classification process for each device type:

Task A: Collect existing scientific information in the public domain and/or from scientific experts in the medical community and assess the risks versus benefits of the medical device type subject to the classification;

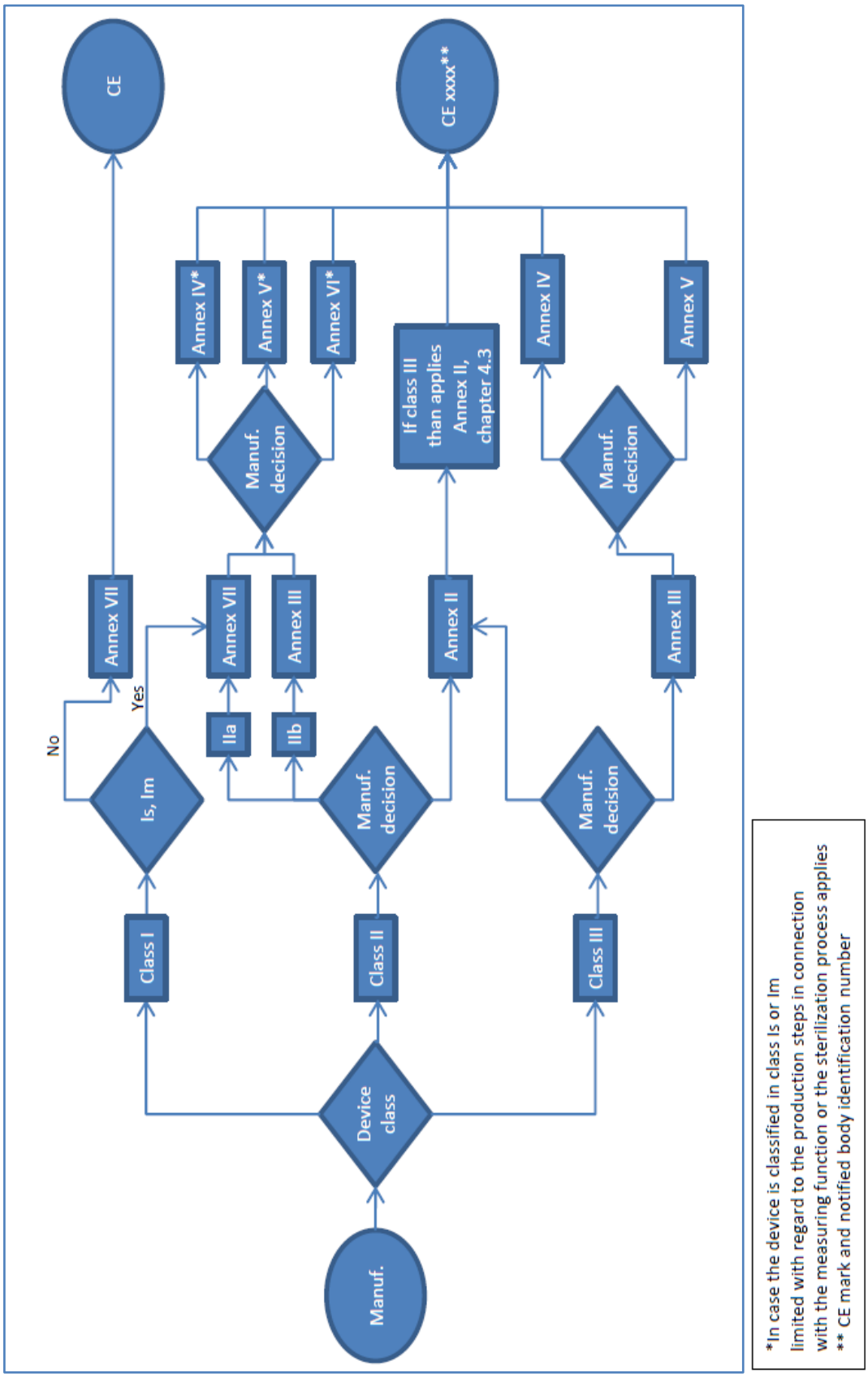
Task B: Convene a meeting of the medical device advisory committee (panel) to request input on the classification of the device type;

Task C: Issue a proposed order (proposed classification) reclassifying the device type into Class I or II, or, if retaining the device in class III, calling for a PMA;

Task D: Review and consider comments submitted by the public;

Task E: Issue a final order (final classification) reclassifying the device type into Class I, or II, or, if retaining the device in class III, calling for a PMA.

Appendix K - Conf**o**rmity assessment processes per MDD (cf. Bayrisches Staatsministerium für Wirtschaft, Infrastruktur, Verkehr und Technologie, 2012 Stand 2)



Appendix L - Overview of the contents of the Annexes II to VII of COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

Annex II – Full quality assurance system
The manufacturers Quality system covers design, manufacturing and final inspection of the medical device. The manufacturers Quality system is subject to audits. In addition, the device is subject to the market surveillance. The CE marking as required in Article 17 of the MDD has to be affixed on the device upon issuance of the declaration of conformity by the manufacturer. In addition to the Annex II.3 obligations mentioned above, manufacturers of Class III devices must apply for an examination of the device design dossier by the Notified Body.

Annex III – EC type examination
The Notified Body certifies that a representative production sample fulfills the MDD requirements. The CE marking as required in Article 17 of the MDD has to be affixed on the device upon issuance of the declaration of conformity by the manufacturer.

Annex IV - EC verification
The manufacturer / authorized representative declares that the device that has undergone the procedure set out in section 4 of the Annex IV complies to the type listed in the EC type examination certificate and that it meets the MDD requirements. The CE marking as required in Article 17 of the MDD has to be affixed on the device upon issuance of the declaration of conformity by the manufacturer.

Annex V - Production quality assurance
The manufacturers Quality system covers manufacturing and final inspection of the medical device. In addition, the device is subject to the market surveillance. The CE marking as required in Article 17 of the MDD has to be affixed on the device upon issuance of the declaration of conformity by the manufacturer.

Annex VI – Product quality assurance
The manufacturers Quality system covers testing and final inspection of the medical device. The manufacturers Quality system is subject to audits. For sterile devices the manufacturing process must ensure and maintain the sterility of the device. The CE marking as required in Article 17 of the MDD has to be affixed on the device upon issuance of the declaration of conformity by the manufacturer.

Annex VII – EC declaration of conformity
The manufacturer / authorized representative declares that the device fulfills the MDD requirements and affixes the CE-Mark on its device. Please note, this Annex is only applicable to low risk devices.

Appendix M – Overview of the three types of a 510(k)

The Traditional 510(k) is the original submission method defined in 21 CFR Part 807 Subpart E and by section 510k of the FD&C Act. These US regulations require that the FDA has to be notified by manufacturers who must register their business with FDA 90 days prior to introducing a device to the US market. This is applicable to novel devices and marketed devices that were changed in that way that could have influenced their safety or effectiveness and therefore need to be reintroduced. 21 CFR Part 807.87 defines the elements that need to be included in a premarket notification submission. After 510(k) clearance, the FDA may inspect the facilities used to design or manufacture the device at any time to review the Quality system of the manufacturer (21 CFR 820).

The Abbreviated 510(k) is an option for manufacturers where FDA guidance documents have been used in manufacturing, special controls as defined in FD&C Act section 513(a)(1)(B) have been implemented or standards have been used in manufacturing that are recognized by the FDA. To speed the FDA review, manufacturers must supply summary reports describing the implementation of standards / special controls or manufacturer declaration of conformity to the recognized consensus standards that have been applied (cf. Food and Drug Administration [6], 2009). Like the Traditional 510(k), the Abbreviated 510(k) also must contain the elements defined in 21 CFR Part 807.87. Test data also might be requested by FDA.

The Special 510(k) is only used to submit to the FDA certain modifications that were made to a device that already has achieved 510(k) clearance. This type of a premarket notification uses the design control requirements of 21 CFR Part 820.30. Except for the declaration of conformity to design controls, no further design data need to be submitted.

Appendix N - Different methods of a PMA

❖ Traditional PMA

A device which already has achieved approval in a highly regulated country and that can present valid data from clinical testing may submit the PMA in one complete application file.

❖ Modular PMA

The complete volumes of data and information in a PMA application are separated into modules. Upon the completion of each module, it is submitted to the FDA for prompt review. This enables the manufacturer to respond to potential deficiencies in the timeliest possible manner. This PMA method is interesting for applicants that have their device in an early clinical trial phase.

❖ Streamlined PMA

A Streamlined PMA may be used for devices with technologies and applications that are familiar to the FDA and for which FDA guidance documents exist, or when the FDA already has reviewed more than one similar device. The pilot program enables gaining device market access as soon as possible. However, a full PMA application is required for a Streamlined PMA.

❖ Product Development Protocol (PDP) PMA

Manufacturers of devices whose technology is well known in the medical industry should give consideration to the use of a product development protocol (PDP) PMA as defined in 21 CFR Part 814.19. In this method, the FDA and applicant work closely together especially in the design and development phase to agree to required actions that will prove that the device is safe and effective.

Appendix O - Steps in the PMA Application Process (cf. Food and Drug Administration, 2011)

- Office of Device Evaluation filing review
- Office of Surveillance and Biometrics statistical review for filing
- Office of Compliance review of manufacturing information for compliance with the Quality System regulation (21 CFR 820).
- PMA decision filing
- Day-100 Meeting
- Quality System Inspection(s) by the FDA field personnel. An FDA manufacturing inspection is conducted for all original PMAs and may be conducted for PMA supplements requesting approval of alternate or additional manufacturing and sterilization facilities.
- Bioresearch Monitoring (BIMO) Audit (audit of clinical study data)
- Substantive review coordination and completion in areas such as:
- Preparation of FDA Summary of Safety and Effectiveness Data (SSED)
- Nonclinical Studies
  [Microbiological, Toxicological, Immunological, Biocompatibility, Shelf Life, Analytical (for IVDs), Animal, Engineering (Stress, Wear, Fatigue, etc.)]
- Clinical Studies
- Panel Meeting Decision and Mailing (if panel meeting is appropriate)
- Panel Date (if appropriate)
- Transcripts Received, Reviewed and Placed in Administrative Record
- QS/GMP Clearance
- Final Response from OC for GMP/BIMO
- Final ODE Decision Memo
- Approval Package, Approval Order, SSED, Final Draft Labeling

Appendix P - Outcomes of the PMA review process

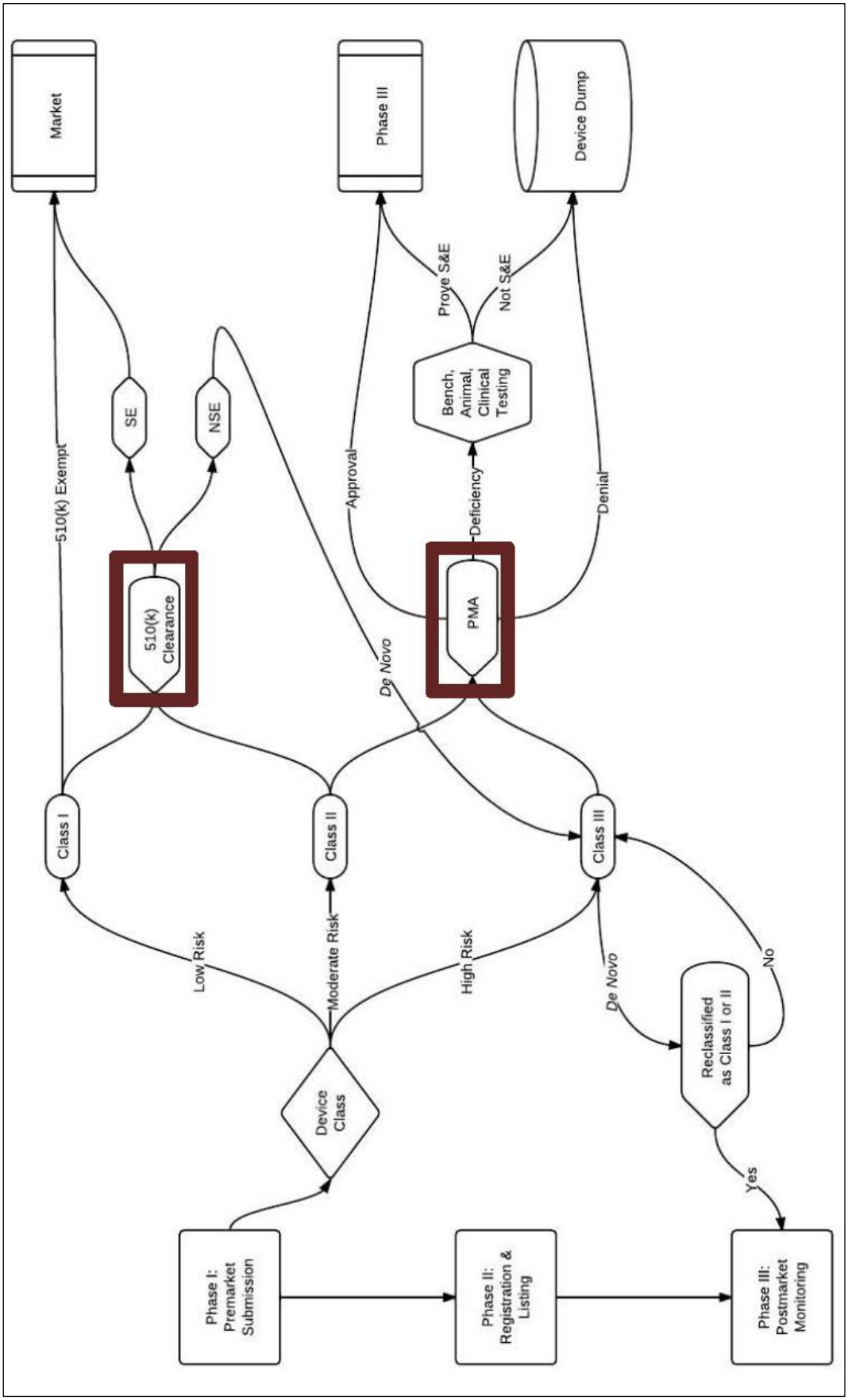
- Approval order (21 CFR Part 814.44(d)),
  - An Approval Order will be issued if none of the causes stated in §814.45 applies. Prior to the applicant is allowed to market the device, the applicant must submit the final labeling.

- Approvable letter (21 CFR Part 814.44(e)),
  - The PMA meets the defined requirements adequately but some additional information is requested, or specific conditions need to be agreed prior the final approval. The approvable letter identifies the open items.

- Not approvable letter (21 CFR Part 814.44(f)),
  - Because of one or more causes as identified in §814.45(a) or due missing important information the FDA believes the PMA is not approvable. The not approvable letter outlines the reasons for the non-approval, or identifies the actions to make the PMA approvable. The applicant may amend the PMA, may request administrative review or withdraw the application.

- Order denying approval (21 CFR Part 814.45),
  - The FDA denies a PMA if the applicant did not met the PMA requirements or because the FDA identifies reasons for denying approval as specified in section 515(d)(2)(A)-(E). Other reasons for denying approval are: false statements, wrong labeling and applicant refuses FDA inspections or denies copying of documents, non-compliances in clinical trial conduction. The denial letters outlines the reasons for the denial and if worthwhile identifies the actions to make the PMA approvable.

Appendix Q - FDA review procedures (cf. Liu, 2012)



Appendix R - Examples for the content of the technical file according to the Annex VII of the COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices

- Title, Table of contents, Revision history
- Name and Address of the manufacturer
- Name and Address of the EU representative
- Product description including its purpose and types
- Engineering drawings and descriptions
- List of standards referenced in the file
- Risk management documents
- For sterile devices: description of sterilization methods and validation report
- Testing results
- Finite Elements calculations
- Clinical data report
- Instruction for use
- Labeling
- Overall manufacturing and inspection plan
- Declaration of conformity (signed)
- Essential requirements checklist
- List of manufacturing sites

Appendix S - Examples for: Procedures required by the MDD; and Procedures required by the DIN EN ISO 13485 standard

Examples of procedures and contracts typically required by the MDD:

- Medical device reporting;
- Technical file / design dossier and maintenance;
- Declaration of conformity and overview of CE-marked devices;
- Clinical data / clinical investigation;
- Nomination of an authorized EU-representative, if applicable;
- Translation of labeling and translation verification;
- Notification of the Notified Body (e.g. with regard to substantial changes to the Quality system or covered device range);
- EU representative contract;
- Key supplier contracts; and
- Distributor contracts.

Additionally, the list below provides examples of DIN EN ISO 13485 procedures typically required:

- Management review;
- Contract review;
- Job descriptions;
- Change notice procedure;
- Complaint handling and trending;
- Non-conformity trending;
- Internal audits;
- Pest control;
- Facility cleaning procedure (e. g. warehouse) and
- Computer system backup procedure.

Appendix T - Samples of typically required GMP procedures

Samples of typically required GMP procedures:

- Design controls;
- Document control;
- Purchasing control;
- Identification and Traceability;
- Records (e. g., complaint files);
- Acceptance activities (e. g., finished device acceptance);
- Servicing;
- Production and Process controls (e. g., process validations); and
- Labeling and packaging control.

Appendix U - Pre-and Post-marketing requirements in Germany; and in the USA

Premarketing requirements in Germany

- *Labeling in accordance to §11 no. 2 and §5 of the German law on medical devices (MPG)*

According to §5 of the MPG it is mandatory to display the name / company and the address, of the person (e.g., manufacturer or authorized representative) responsible for device´ first placing onto market, on the device labeling or instructions for use. Further, §11 no. 2 defines that the language of the medical device information that is provided to the user has to be in German, except for reasonable cases. However, all safety relevant information must be provided in German or in the user's language.

- *The obligation of notification per § 25 of the German law on medical devices (MPG)*

The German Law on medical devices requires per § 25 no.1-3 the notification of the federal competent authority about the first placing of a medical device onto the market. This is applicable to those persons (which are responsible for the device´s first placing onto market) that are based in Germany. The meaning of "first placing on the market" is defined in MPG §3 no.11. MPG §5 defines the person responsible for the device´ first placing onto market. The requirement is based on article 14 of the MDD.

- *Requirements for clinical evaluation, performance evaluation and clinical trials per §§19 to 24 of the German law on medical devices (MPG)*

The § 19 of the MPG requires to show the suitability of medical devices for the claimed intended use in a clinical evaluation. The §§19 to 24 define the requirements for clinical evaluation, performance evaluation and clinical trials.

- *Nomination of a safety officer per §30 of the German law on medical devices (MPG)*

The German Law on medical devices requires per § 30 from the person responsible for the first placing of devices onto market right after beginning with its activities the nomination of an adequately qualified safety officer. The qualification requirements are specified in §30 no.3 and include 2 years work experience and evidence of adequate expertise. There is an obligation to notify the federal competent authority about the nominated safety officer including name and contact data as well as any changes to the safety officer person.

It is an obligation to notify the federal competent authority as mentioned above (§§25 and 30) via the database of the German Institute of Medical Documentation and Information (DIMDI). This is specified in §2 of the DIMDI Decree concerning the database supported Information System of the German Institute of Medical Documentation and Information.

- *Medical device consultant according §31 of the German law on medical devices*

In accordance to §31 MPG only medical consultants are allowed to train health care professionals. To be a medical consultant requires adequate expertise and work

experience as defined in §31 no. 2 MPG. The medical device consultant reports to the safety officer.

- *Prescription status according to the Decree concerning the Availability on Prescription only of Medical Devices (MPVerschrV)*

The Decree regulates the prescription of medical devices. Medical devices listed in the Annex of the Decree and devices which contain medicinal substances or their ingredients are only available on prescription.

- *Decree concerning the Installation, Operation and Use of Medical Devices (MPBetreibV)*

Purpose according §1 of the MPBetreibV is to regulate the installation, operation, use and maintenance of medical devices defined in §3 of the MPG for prevention of accidents and any hazards. The decree applies to all persons and institutions that install, operate, use or maintain medical devices in a professional way. Exceptions are defined in §1 no. 2 MPBetreibV.

- *Registration requirement as per Electrical and Electronic Equipment Law (ElektroG)*

Under the terms of this law those manufacturers and distributors who intend to market or distribute any electrical and/or electronic apparatuses are stipulated to register online with the competent authority.

- *Decree on Distribution Channels for Medical Devices (MPVertrV)*

The decree defines medical devices that must be sold via pharmacies and specifies exceptions to this distribution channel.

Premarketing requirements in the USA

- *Establishment registration and device listing as per 21 CFR Part 807*

As per 21 CFR Part 807.20, manufacturers of medical devices, owners / operators of an establishment that manufactures, prepares, propagates, assembles, processes, etc. of a device, are required to register their establishments and to submit a device list once a year (cf. Food and Drug Administration [11], 2012). Activities of domestic and foreign manufacturers which require establishment registration and listing are listed below (cf. Food and Drug Administration [11], 2012):

- Manufacturers, foreign Manufacturers, custom made device manufacturers, contract manufacturers, contract sterilizers, contract packagers, domestic manufacturers of export only devices
- Specification Developers, Repackagers or Relabelers, manufacturers of components or accessories directly sold to end users, Reprocessors of single-use devices, Remanufacturers, foreign Exporters.

Below are two characteristics of the establishment registration and listing described (cf. Food and Drug Administration [11], 2012):

- Domestic initial importers must only register their establishment.
- Foreign manufacturers located outside the US must appoint a US Agent within the establishment registration process.

Furthermore:

- Premarket Notification as per 21 CFR Part 807 Subpart E
- Premarket Approval as per 21 CFR Part 814
- Investigational device exemption as per 21 CFR Part 812
- Labeling as per 21 CFR Part 801 - The device must be adequately labeled in accordance with 21 CFR Part 801.
- Quality system regulation (QSR) / Good manufacturing practices (GMP) as per 21 CFR Part 820

Post marketing requirements in Germany

- *Medical device vigilance procedure as required per MPG and as defined by MPSV*

The most important post marketing requirement for the manufacturer is the medical device vigilance procedure. Through § 29 no.1 MPG and the Decree on a Medical Devices Vigilance System (MPSV) Germany has implemented article 10 of the MDD. Article 29 no.1 of the MPG defines the tasks and responsibilities of the competent federal authority[42] within the medical device vigilance procedure.

The medical device vigilance procedure is conducted through the MPSV. According to §1 MPSV, the scope of the MPSV is the regulation of procedures with the purpose of collection, evaluation and control of risks that may occur by the use of medical devices. Within this decree reporting requirements for incidents and recalls (as per §§3-7), reporting requirement exemptions (as per §4), reporting timelines (as per §5), reporting modalities (as per §7), the obligation to co-operate with the competent authority (as per §12) and the performance of corrective actions (as per §14 MPSV and §5 MPG) are defined.

Others

- Pricing and reimbursement of medical devices in accordance with German Social Code IV (SGB V)
- Advertising and promotion of medical devices according to the Law on Advertising in the Field of Healthcare (HWG)
- Notified body surveillance and recertification audits (MDD)

[42] The main competent federal authority for medical devices is the BfArM, the PEI (Paul Ehrlich Institute) is responsible for certain in-vitro diagnostics

Post marketing requirements in the USA

- *Medical device reporting as per 21 CFR Part 803*

One of the most important post marketing requirements for manufacturers, importers, distributors and device users is the medical device reporting as defined in 21 CFR Part 803. The 21 CFR Part 803.1 outlines the general application of the reporting requirements. Thus, manufacturers must report certain device related events and malfunctions of a device. Furthermore, manufacturers must record adverse events and must provide follow up reports to the FDA. Subpart B of the 21 CFR Part 803 outlines the reporting requirements for Individual Adverse Events while subparts C-D specify the reporting requirements to device user facilities, importers and manufacturers in detail.

Others

- Reports on recalls, corrections and removals as per 21 CFR Part 806, 21 CFR Part 810 and 21 CFR Part 7
- Post market surveillance studies for certain class II / class III devices as per FD&C Act section 522 (21 CFR Part 822)
- Medical device tracking as per 21 CFR Part 821
- Quality system regulation (QSR) / Good manufacturing practices (GMP) as per 21 CFR Part 820
- GMP inspections by FDA personnel or accredited persons

For PMA approved devices following additional post marketing requirements apply:

- Annual reports as per 21 CFR Part 814.84
- Adverse reaction and device defect reporting as per 21 CFR Part 814.82(a)(9)
- PMA supplement as per 21 CFR Part 814.39
- Post-approval studies
- Post-approval inspection

Appendix V - General considerations for the marketing of medical devices

Summary for Germany / EU

In summary, the items listed below should be considered when it is desired for a medical device gaining market access to the German / European market:

- Manufacturer determines if the product is a medical device.
- Manufacturer determines which of the three main Medical Device Directives applies.
- Manufacturer classifies the device.
- Manufacturer chooses the conformity assessment process based on the Class of the device.
- Manufacturer chooses the Notified Body.
- Manufacturer implements a Quality system.
- Manufacturer generates and collects data necessary for technical file / design dossier documentation.
- Manufacturer prepares the technical file / design dossier documentation.
- If applicable, the manufacturer appoints an EC representative.
- Manufacturer verifies that the device is in compliance with the applicable essential requirements.
- If applicable, the chosen Notified Body performs the device certification using the selected conformity assessment form and issues an EC-certificate. No Notified Body assessment is necessary for Class I devices as the manufacturer performs the conformity assessment
- If applicable, the Notified Body certifies the Quality system by issuing a Quality system certificate.
- Manufacturer prepares and signs the declaration of conformity.
- Manufacturer reports to the competent authority the person who is in charge of placing the medical device on the market.
- Manufacturer affixes the CE-Mark on the device.

Summary for the USA

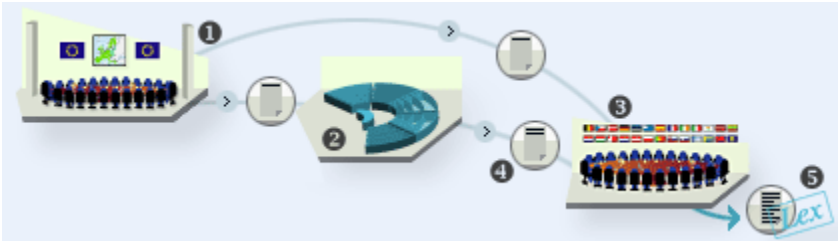
In summary, the items listed below should be considered when it is desired for a medical device gaining market access to the US market:

- Manufacturer determines if the product is a medical device.
- Manufacturer classifies the device. Device class defines the regulatory review process to obtain market approval.
- Manufacturer decides which type of 510(k) or PMA application is the most appropriate.
- Manufacturer implements a Quality system to be in compliance with the GMP requirements.
- Manufacturer generates and collects data necessary for marketing application submission.
- If a clinical trial is required to collect data, an IDE must be approved by FDA prior to start the clinical trial.
- If a 510(k) is being submitted, manufacturer compiles application information, submits 510(k) and pays 510(k) fee.
- If a PMA is being submitted, manufacturer compiles application information, submits PMA volumes or modules and pays PMA fee if applicable.
- If a 510(k) was submitted, the FDA will send a 510(k) clearance letter and publish the clearance letter on the FDA homepage
- If a PMA was submitted, the FDA will assign a preapproval facility inspection. In addition, the manufacturer must submit the final device labeling to the FDA prior to approval. The FDA will send an approval letter and publish the letter and Summary of Safety and Effectiveness Data (SSED) on the FDA homepage.

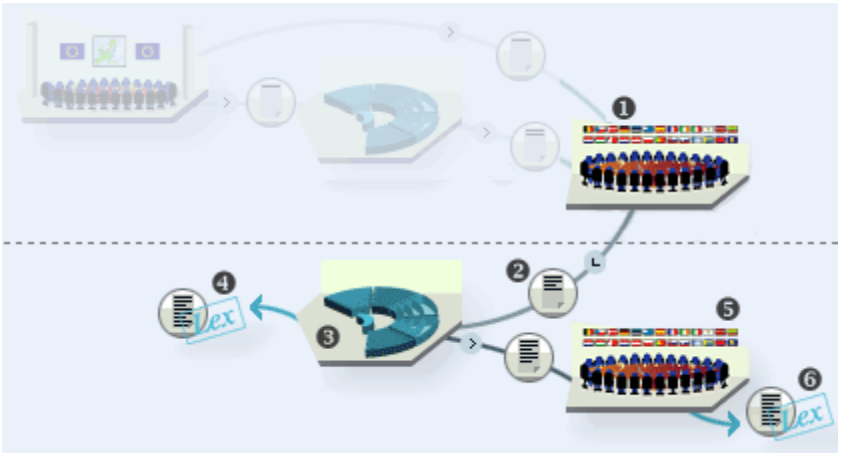
Appendix W - Ordinary legislative procedure (cf. European Parliament, 2009)

The co-decision procedure was introduced by the Maastricht Treaty on European Union (1992), and extended and made more effective by the Amsterdam Treaty (1999). With the Lisbon Treaty that took effect on 1 December 2009, the renamed ordinary legislative procedure became the main legislative procedure of the EU´s decision-making system.

First reading



The (1) Commission presents a legislative proposal to (2) Parliament and the (3) Council simultaneously.
Parliament adopts (4) its position and submits it to the Council.
If the Council agrees with the outcome of Parliament's first reading (5) the legislative text is adopted.
Second reading

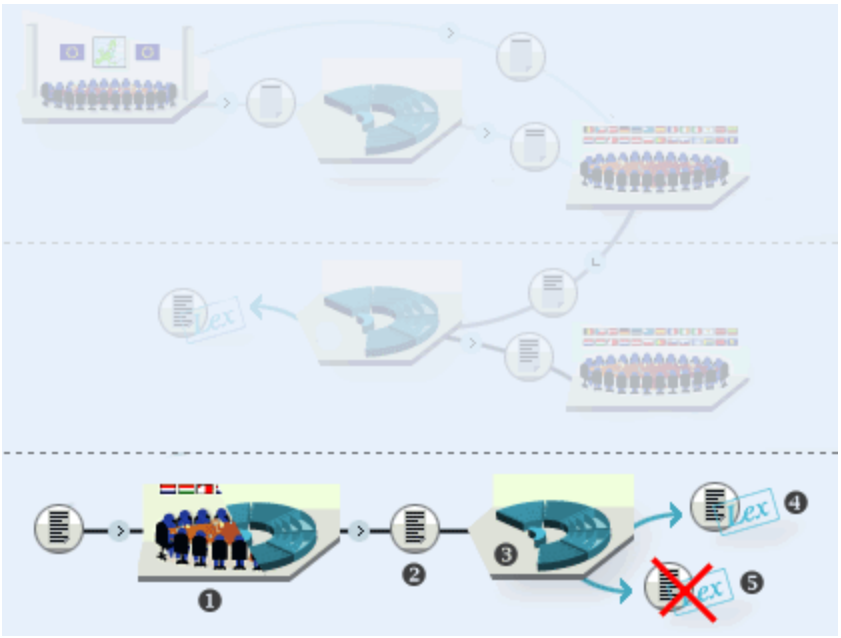


If the (1) Council does not accept Parliament's first reading position, it draws up its (2) position.
(3) Parliament has 3 months (an extension to 4 months can be requested) to react. It may approve the Council position or take no decision and the (4) legislative text is adopted in the form of the Council position
Or Parliament may table amendments to the Council position (subject to certain restrictions). In this case:

- either the (5) Council, within 3 months (an extension to 4 months can be requested) approves Parliament's amendments, and the (6) legislative text is adopted

- or the Council rejects them, and a Conciliation Committee (27 Members of Parliament and 27 Members of the Council) is convened to seek to reconcile the positions
- Alternatively, Parliament may reject the Council position by an absolute majority of its members, in which case the legislative text is rejected

Conciliation and third reading



After an agreement has been reached, the (1) Conciliation Committee adopts a (2) 'joint text' based on the Council position and the EP's second reading amendments.
If the Council and (3) Parliament approve the 'joint text' in its entirety, the (4) act is adopted.
If the Conciliation Committee cannot agree on a 'joint text', or if Parliament or the Council does not approve it, the (5) act is deemed not to have been adopted.

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Taufkirchen, den 03.05.2013

Unterschrift