

**The Humanitarian Device Exemption of the United
States as a Pioneering Concept in Orphan
Device Regulation and its Implications for the Policy
of the Regulation of Medical Devices for Small Popu-
lations in the European Union**

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LIST OF ABBREVIATIONS AND ACRONYMS

AIMDD	Directive on Active Implantable Medical Devices
CDRH	Center of Devices and Radiological Health at the FDA
CE	Conformité Européenne
CFR	Code of Federal Regulations
COMP	Committee for Orphan Medicinal Products
EC	European Community
EEA	European Economic Area
EMA	European Medicines Agency
EUCOMED	European Medical Device Industry Advocacy Organization
EUROPLAN	European Project for Rare Diseases National Plans Development
EUDAMED	European Databank on Medical Devices
EU	European Union
EURORDIS	European Organization for Rare Diseases
FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FD&C Act	Federal Food Drug and Cosmetic Act
HMD	Humanitarian Medical Device
IDE	Investigational Device Exemption
IRDiRC	International Rare Disease Research Consortium
IVD	In-Vitro-Diagnostic
NB	Notified Body
NES	Non Essential Similarity

NORD	National Organization for Rare Disorders
ODA	Orphan Drug Act 1983
OOPD	Office of Orphan Products Development
PMA	Premarket Approval
RCT	Randomized Controlled Clinical Trial
U.S.	United States
WHO	World Health Organization

1 Introduction

This thesis aims to analyze aspects of the regulatory premarket pathways in the European Union (EU) and the United States (U.S.) regarding medical devices intended for use in rare diseases and conditions. The specificities of rare diseases are primarily the limited number of patients and scarcity of expertise [11]. These medical products are referred to hereafter as “orphan devices” in analogy to “orphan drugs”, recognizing that they are less likely to be developed by industry because the market is small, and research and development costs usually cannot be compensated through market revenues. The following analysis will outline the United States’ FDA pioneering concept of Humanitarian Use Device (HUD)/ Humanitarian Device Exemption (HDE), specifically designed to accelerate the market access of orphan devices under the condition of continuous additional approval of a local investigational review board. As there is no comparable regulatory pathway implemented in the EU, the question is raised, whether any elements of the FDA’s concept may be applicable as a model for tailored legislation in the EU. The necessity to accelerate orphan device development in the EU has been stated by the EU umbrella patient advocacy organization for rare diseases, EURORDIS. It underlined the significance of orphan devices and proposed the implementation of the label “Humanitarian Medical Device” (HMD) [1]. As relevant structural differences between the two regulatory systems in the EU and U.S. have to be taken into account in judging about the transferability, critical elements of both are briefly described with emphasis on the premarket assessment of novel high-risk therapeutic medical devices.

2 Research Objectives

With the enactment of the humanitarian use device/ humanitarian device exemption concept by U.S. Congress in 1990, the United States’ federal law through the Safe Medical Devices Act of 1990 (P. L. 101-629) governs a regulatory framework recognizing the specific constraints and financial burden of the development of medical devices intended for rare disease populations [2]. This concept, the first of its kind concerning medical devices, eventually became necessary due to emerging technical progress and invention on the sector of medical devices. The patient’s access to novel devices incorporating new materials, complex technical features or that are targeting unmet medical needs, is highly impacted by premarket clinical data re-

quirements. The premarket assessment procedure therefore is a critical milestone in any device development project. Concerning products with low revenue expectations, the project may be ended prematurely by the manufacturer due extension of costs. Moreover, with regard to the small numbers of patients affected by a specific disease or condition, the conduct of large clinical studies may not be feasible in some cases. Eventually U.S. Congress became aware of the impediments of the approval threshold for potentially meaningful medical devices bearing new technologies in terms of health care value also for rare diseases. In order not to exclude patients with rare diseases or conditions from the adoption of technical innovation, a non-standard premarket procedure was implemented with the HUD/ HDE pathway.

To illustrate potential rare medical targets for medical devices, three conditions and diseases from two different therapeutic areas are presented as case studies in section 9.7.3: Pediatric heart failure (cardiology), dystonia and cranial stenosis (both neurology).

In this thesis, devices intended for small populations are referred to as “orphan devices” in analogy to “orphan drugs”. Nevertheless, particular requirements associated with the development and market access of orphan devices are distinct from those for orphan drugs. The assumption is, that a tailored regulatory policy for orphan devices will be necessary in the EU in order to foster their market access, since there currently is no corresponding concept established.

Based on a comprehensive evaluation of the current regulatory premarket environments for therapeutic high risk medical devices in the United States and the European Union, this review will explore the suitability of the FDA’s HDU/HDE concept to serve as a model for the EU.

Taking into account the endeavor undertaken by the United States’ FDA to accelerate the development of products classified as humanitarian use devices (HUD) for almost two decades, it can be assumed that there are relevant unmet medical needs regarding medical devices although until today, no comprehensive database exists but may be created in the near future.

Medical devices cover a very wide range of products for imaging, surgical instruments, respiratory devices, active implantable devices, for example. In comparison to the U.S., the EU orphan devices seem not to have been an issue until today. Accord-

ing to the communication of the European Commission with regard to the „Action Plan for Rare Diseases“, orphan devices have not been considered for taking action to present.

However, the German Ministry of Health published a report on the topic of adequate medical care with medical devices recently, the HDU/HDE concept was mentioned in the context of the proposal of and EU Medical Device Regulation. The report points out that the FDA’s concept should be assessed with regard to the EU modeling a specific regulatory scheme after it [3, 4].

In rare conditions, the process of clinical data generation may sometimes be waived until postmarket phase due to small patient numbers, and more regulatory flexibility may be necessary.

The identified concepts will be tested with regard to the European regulatory system for medical devices. Until today, there is no legal term “orphan device”. With the advent of the Medical Devices Regulation, this gap may inhibit clinical investigation and consequently market access of orphan devices. This question will be approached.

3 Methods and Materials

Two systematic literature researches were performed in EMBASE. For the first one the following search terms were applied in permuting combinations: „medical device“ AND „orphan“ OR „rare disease“ OR „rare condition“ AND/OR „FDA“ AND/OR „Europe“. This search delivered very few results. This was interpreted as an indication that the topic probably has not been focused on in the past.

Therefore, a second systematic research was conducted using search terms less specific for medical devices, but aiming at retrieving results on more general aspects with regard to rare diseases: “policy“ AND „rare disease“ OR „rare condition“ OR „United States“ OR „European Union“. Again, only a few articles were retrieved. Along with the first search, they served as starting points by utilizing their references for further literature search. A relevant source of information regarding U.S. legislation and procedures, information was retrieved from FDA’s homepage. In addition, established publishers and journals of the biomedical engineering sector were systematically searched for the terms “rare”, “disease*”, “condition”, “orphan”, “device”, “medical”, “medtech”, “regulation”, “law”, “policy” in any possible combination. Among

the sources were: The Journal of Medical Device Regulation; Medical Device Reviews; Nature; The Lancet; Axel Springer publishing house and Informa Healthcare and the U.S. National Academies Press. Only three journal articles were identified that specifically dealt with “orphan devices” at all. It is therefore assumed, that there has been only little interest in this issue from the perspective of regulatory science at all until today.

4 Milestones of the Implementation Processes of Policies on the Regulation of “Orphan Products”

4.1 The Concept of Rare Diseases

A rare disease is a disease with a low prevalence. In the United States, a rare disease is defined as disease affecting small patient populations, typically less than 200,000 people in the United States per year as stated in the Rare Diseases Act 2002 (P. L. 107–280). In the European Union, rare diseases are described as life-threatening or chronically debilitating diseases that have a prevalence of 5 out of 10.000 individuals or less [11].

There are 7000 diseases considered rare. In the EU an estimated 25 million people suffer from one. In the U.S. almost 30 million individuals are affected. Effective treatment options exist only for a few rare diseases, whether by chance or due to the commitment of patient advocacy. For most rare diseases, there is a lack of even simple basic knowledge. The cause of the diseases, their frequency, prognosis and heritability is usually unknown. Therefore rare diseases collectively account for significant unmet health care needs in the United States and Europe [2, 8, 12]. In parallel with the evolution of regulatory systems for drugs and medical devices that heavily rely on premarket testing, the development costs have been rising. For products with expectedly smaller market returns, even below the investment, an impediment was created through the extensive data requirements for market approval. Consequently, product development for small markets was less attractive for industry and therefore “orphanized”. The U.S.’s National Institutes of Health estimates that 50 percent of the patients affected by a rare disease are children and only 30 percent of them will celebrate their fifth birthday [13,14]. Nevertheless, barriers to the availability of pediatric devices are frequent and significant [11]. Particularly in the cardiac, pulmonary and orthopedic therapeutic areas pediatric devices are needed. “Despite the tremendous

success of the Orphan Drug Act, rare diseases and disorders deserve greater emphasis in the national biomedical research enterprise.” [5].

4.2 European Union

4.2.1 EU Orphan Drug Regulation of 1999

In 1999 in the EU Regulation (EC) No 141/2000 was enacted [8]. The scope was limited to drugs intended to treat rare diseases that were life-threatening or chronically debilitating. The regulation set out a statutory definition for rare diseases, based on the prevalence rate that was not to exceed 5 in 10.000 individuals in the EU. A drug was also to obtain an orphan drug designation, if the sponsor could establish that the investment into development could not be compensated by market returns (financial criteria). Accordingly, provisions were enacted for the financial promotion of research, development and the placing on the market of promising orphan drugs. The provisions are of incentive character companies may choose to take advantage of them. A scientific Committee for Orphan Medicinal Products (COMP) was implemented at the European Medicines Agency (EMA) with this regulation in order to review applications for orphan drug designations.

4.2.2 Communication from the European Commission 2008

Another crucial legal instruments addressing the complex issues associated with rare diseases in a harmonized manner, is the European Commission’s policy on rare diseases as stated in the Communication on Rare Diseases in 2008. This serves as a framework to each member state’s national action plans. However, regarding orphan devices it states: “The Orphan Medicinal Product regulation does not cover the field of medical devices. The limited size of the market and the limited potential return on investment is a disincentive. The Commission will assess whether there is a need for measures to overcome this situation, possibly in the context of the forthcoming revision of the Medical Device Directives” [23].

4.2.3 Implementation Report from the European Commission 2014

The report reveals in its conclusion that “the Commission has fostered the exchange of experiences to help Member States develop their national plans or strategies for rare diseases [16]. This has supported a significant number of Member States to put in place dedicated plans to address rare diseases: Sixteen Member States now have rare diseases plans (as compared to only four in 2008) and a significant number are

close to adopting a plan. Supporting Member States in this endeavour remains the key priority for the Commission's work in this area. Despite such encouraging progress, there is still a long way to go to ensure that people suffering from a rare disease can obtain the right diagnosis and best possible treatment throughout the EU.” Therefore, the EU Commission clarified on their focus in the matter: fostering national rare disease plans. But awareness of different tasks is also expressed in the document: “Work further to decrease inequalities between patients with rare diseases and patients suffering from more common disorders and to support initiatives promoting equal access to diagnosis and treatment.” [16]. Nevertheless, the documents lack a commitment to “orphan devices”. It thus is plausible to conclude that the potential value of medical devices to health has not been perceived sufficiently.

4.3 United States of America

4.3.1 United States Orphan Drug Act of 1983

The policy of the U.S. federal government aiming to assist in the development of products for the diagnosis, prevention or treatment of rare diseases or conditions was ruled with the Congress passing the Orphan Drug Act in 1983 (P. L. 97-414) [27]. Incentives were provided to the industry for the investment in therapies for rare diseases, sometimes referred to as “orphan products”. The FDA Office of Orphan Products Development (OOPD) was implemented through this legislation with the mission to advance the evaluation and development of products (e.g. drugs and medical devices) that demonstrate promise for the diagnosis and or treatment of rare diseases or conditions [30]. The OOPD evaluates scientific and clinical data submissions from sponsors to identify and designate products as promising for rare disease and to further advance their development. The office also works on rare disease issues with the academia, other governmental agencies, industry, and rare disease patient groups and through these means implements the US’s rare disease policy aiming to accelerate patient’s access to orphan products. The OOPD also provides grants for clinical studies on safety and/or effectiveness that may either result in, or substantially contribute to, market approval of these products. The mission of FDA’s Orphan Products Grants Program in the OOPD supports, among other products, the clinical development of medical devices for use in rare diseases and conditions where no current therapy exists, or if the device is expected to be superior to established treatment options.

The many barriers to the development and availability of medical devices intended for the pediatric population lead to the implementation of the Pediatric Device Consortia Grant Program at the OOPD, which provides funding to nonprofit consortia to facilitate the development of pediatric medical devices, which often are intended for rare diseases and conditions in children (42 USC § 284h) [32, 33].

4.3.2 Humanitarian Use Device and Humanitarian Device Exemption

In 1990, the US Congress authorized the Humanitarian Use Device (HUD) designation and Humanitarian Device Exemption (HDE) pathway to further encourage the invention and development of orphan devices, perhaps owing to the fact that several rare diseases or conditions can only be addressed using medical devices [34, 35]. With this concept, a non-standard regulatory pathway was enforced creating opportunity for access to medical devices intended to address unmet medical needs in rare disease populations that would otherwise not be feasible [14]. A detailed description and analysis of this regulatory concept is outlined in section 9.7.

4.4 The Impact of Patient Advocacy

In both regions, many small patient advocacy groups form umbrella organizations as the European Organization for Rare Diseases (EURORDIS) in the EU and National Organization for Rare Disorders (NORD) in the U.S. The rare disease community consists of people committed to advancing scientific medical knowledge in rare diseases. Advocating on behalf of them are among others, patients and their families, health care professionals and government officials. They are frequently united by the knowledge and experience with sick children going through a difficult diagnostic odyssey and then learning the fact that there is no therapy for them [38,]. EURORDIS emphasizes that medical devices in rare diseases patients often provide a major contribution to life expectancy and quality of life [1, 40].

EURORDIS statement in the context of Recast of the Medical Device Directive: "...proposing the creation of a regulatory status of "Humanitarian Medical Device" for the EU, due to the relevance of medical devices in the context of rare diseases." [1].

5 Common Principal Elements of Medical Device Legislations in the EU and the U.S.

In general, the challenges to medical device regulation are similar, independently from the global region it will apply to. Especially in the EU and the U.S. common principal elements are shared regarding aims and legislation. Nevertheless, as outlined in chapter 9 and 10, the implemented procedures vary significantly, particularly the rules for premarket assessment. Due to the vast range of medical devices and their broad range of intended purpose and technical features, the risks to human use are ranging from non-significant to high-risk to human life. Medical devices share with drugs the intended medical purpose, but differ in the means to achieve it. The legislative frameworks for medical devices in the U.S. and the EU are more recent than the regulatory frameworks for drugs and correspond to the enormous technical progress in the field of medical devices. As also further explained in chapters 9 and 10, comprehensive rules for medical devices were enacted in the U.S. in 1976 through the Medical Device Amendments (P.L. 94-295) [41], and during the 1990s through three complementary directives in the EU. Due to the unifying global market, harmonization to medical device regulation is crucial. In this spirit WHO is actively involved and published interesting guidance documents and hosts the “WHO Global Forum on Medical Devices” [42, 43].

5.1 Terminology

Medical device terminology is crucial with regard to the decision whether medical device regulation applies or not. Due to the medical intent shared by drugs and devices, the borderline between both regulated medical product groups is sometimes not evident, and the demonstration of applicability of the terminology’s criteria sometimes can be burdensome to the manufacturer, but also to the regulating body in taking a regulatory decision. According to the WHO, the primary goal is to protect public health and safety [44].

5.1.1 World Health Organization Terminology

The WHO’s international guide on a „A Model Regulatory Program for Medical Devices“ proposes, that a medical device is an „instrument, apparatus, machine, implant or in-vitro reagent whose use is intended for the diagnosis of disease, or for cure, mitigation, treatment or prevention of disease, or for affecting the structure or function of the body for some medical purpose.“ [42]. It specifies, that devices „do not achieve

any of their purposes by means of chemical action within or on humans, and are not dependent on being metabolized to achieve a result.“ [42].

5.1.2 European Union Terminology

A medical device shares with drugs the human medical purpose and may be distinguished from them by the primary mode of action as specified objectively by the manufacturer. According to Article 1.2 of the Directive 93/42/EC, the medical purpose as intended by the manufacturer may not only be therapeutic, but also diagnostic, preventive or other. A medical device can be “any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software”. The principal intended action of a device is not achieved “in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means”.

5.1.3 United States Terminology

The terms to which the U.S. FDA is authorized to determine whether a product is classified as a drug or medical device are defined in the Federal Food D (FD&C Act) §§ 201(g) and 201(h) . The decision has to be based on scientific knowledge about the critical characteristics of the product and the statutory definition:

“A medical device is "an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,

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

intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of 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 any of its primary intended purposes according to 21 USC § 321 (h)).

Therefore, medical devices do not achieve their principal intended action by pharmacological, immunological or metabolic mode of action.

5.1.4 Combination Products

5.1.4.1 European Union

EU legislation does not define a category of drug/device combination products, but assign them to either drug or medical device regulation, depending to the primary mode of action as declared by the manufacturer and taking into account whether the differently regulated components are presented as a fixed combination. By defining the intended primary purpose with regard to the mode of action, the manufacturer specifies his product with regard to the demarcation between medical devices and drugs.

Therefore, a coronary stent with ancillary drug is regulated as a medical device according to Article 2 Nr. 4 of Directive 93/43/EC: “Where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device must be assessed and authorized in accordance with this directive.”

5.1.4.2 United States

Combination products are defined in U.S. legislation as a product category in section 503(g) of the FD&C Act, 21 USC Part 353 (g), 21 CFR Part 3.2(e) and are overseen by the Office of Combination Products of the FDA. The term combination product includes [45]:

- A health care product composed of two or more regulated components and manufactured as one single entity.
- More than one differently regulated components are packaged together into a package unit.
- A drug, device, or biological product is packaged separately that is intended for use only with an otherwise regulated component to achieve the intended use.

5.2 Demarcation of Medical Devices from Drugs

The crucial criteria for distinguishing medical devices from drugs are the mechanism of action and the intended use.

5.2.1 Mechanism of Action

Medical devices differ from drugs in the means through which their healthcare related effect is achieved and are distinguished from for regulatory purpose. Medical devices typically have a physical mechanism of action, while drugs act through chemical (U.S.) [47, 48] respectively pharmacological, immunological or metabolic (EU) principles upon the human body. In case of more than one mechanism of action exerted to the human body, a primary mode of action in contrast to the ancillary mode of action may be identified of the components of combination products. Sometimes multiple modes of action may be involved and sometimes it will be difficult to rank them. Regarding orphan products, the interpretation of the demarcation criteria may have an impact on the eligibility for obtaining an “orphan drug” designation.

5.2.2 Intended Use

By definition, medical devices share with drugs the intended medical use. While drugs usually have a therapeutic effect, medical devices can also be diagnostic in nature or have any other type of effect on the human body (e.g. cosmetic or compensatory for a malfunctioning). The “intended use” has to be specified by the manufacturer in both legislations not only in the instruction for use, but from the beginning of the project of a development process onwards. The technical specifications and performance criteria are tailored regarding the intended use and altogether form an entity with regard to the application of regulatory oversight. The regulatory requirement to demonstrate that the medical device performs as intended is linked to the intended use and therefore can relate to the result of a physical intervention, like denervation for example. If stated by the manufacturer that the medical device was intended to “reduce blood pressure”, this would be the performance goal and the according proof of performance would be equivalent to the demonstration of clinical efficacy. The extent and nature of data required for the clinical evaluation are consequently depending on the intended use specified by the manufacturer. Ultimately, the demonstration of clinical performance may be similar to a proof of effectiveness. The degree of scrutiny of premarket assessment therefore is significantly influenced by the labeling provisions and may be varied by more stringent requirements regarding the instruction for use and specification for the intended use.

5.3 Risk Classification of Medical Devices

The range of medical devices is extensive with regard to their intended purpose and technical features. In order to be able to apply the appropriate level of regulatory scrutiny risk classes have been defined in most regulatory systems [13, 49].

5.3.1 European Union

In the EU, a risk-based classification system applies for medical devices, taking into account the level of risk a device can pose to human health, based on the device's specifications regarding degree of invasiveness, duration of application and degree of interaction with vital organ systems. By applying classification rules, four risk classes are established: I, IIa, IIb and III. The manufacturer has to apply an appropriate conformity assessment route to their product in order to demonstrate that it complies with the essential requirements. He then has to certify the conformity by completing a declaration of conformity.

5.3.2 United States

This risk-related classification designation scheme was a fundamental element of the 1976 law building the basis for application of appropriate regulatory requirements [50].

It is recognized that a higher degree of novelty of applied device technology, implies an uncertainty of risks to a higher extent, unless pre-clinical and clinical data arise to demonstrate reasonable safety. Different regulatory pathways for market access apply according to the designated risk class. The nature and extent of postmarket oversight varies accordingly. The designation of the appropriate risk class therefore is crucial. The appropriate level of control and scrutiny is applied according to the risk class allocated to the medical device, taking into account the degree of „substantial equivalence“ to medical devices legally on the market. In order to demonstrate „substantial equivalence“ to the predicate device, a dossier has to be submitted including technical device characteristic and pre-clinical data (sometimes in-vivo) relating to safety and performance. Usually clinical data are not required for this procedure with the exemption of different new technology being applied to the device. The premarket regulatory pathway of a novel medical device highly depends upon its allocation to one of the risk-classes I, II or III. A device incorporating new technologies is considered a significant risk device, unless otherwise proven, taking into account the high degree of uncertainty with regard to the extent of inherent potential risks associated

with the use in humans. The process of risk-classification strongly relies on the experiences with legally marketed devices to which the “essential similarity” can be established. The FDA is hosting a registry retrieving classification-information for any legally marketed medical device in the US. The manufacturers can make reference to any listed product and make reference to it in their application claiming “essential similarity” to a predicate device that was marketed before the enactment of the MDA in 1978. Consequently, the appropriate level of control and scrutiny may be applied relative to the risk-class the medical device has been designated:

- General controls for class I (low risk, little complexity).
- General and special controls for class II (moderate risk, greater complexity).
- General controls and premarket assessment for class III (significant risk, often life supportive or –sustainable).

In cases when the “essential similarity” cannot be established and “non-essential similarity” (NES) is determined by the FDA instead, the automatic allocation to risk-class III is the consequence. In exceptional cases, the FDA may recommend the “de-novo-procedure” (FFCA Section 513(f)(2)) [9, 7].

For a novel high-risk medical device class III will be allocated if essential similarity to a legally marketed predicate device cannot be established. It will instead be comprehensively tested and evaluated premarket.

5.4 Premarket Review

5.4.1 European Union Premarket Conformity Assessment Procedures

As will be elaborated in section 8.5, the EU legislation provides four different procedures applicable for class III devices according to the annexes II-V of the directives. The conformity assessment procedures are third-party reviews aiming to certify, that the device conforms to the essential requirements. According to a module like concept, the manufacturer can choose from various approaches.

5.4.2 United States Premarket Approval or Premarket Notification

According to U.S. legislation and as outlined in section 9.6, for novel high risk devices, the Center of Devices and Radiological Health (CDRH) of the Federal Food and Drug Administration (FDA) reviews, based on the technical documentation, the manufacture, design history, technical and biological safety data as well as clinical

data derived from approved clinical studies or literature in order to determine whether the manufacturer provided reasonable evidence of safety and effectiveness within the premarket approval (PMA) procedure. In exceptional circumstances, as outlined in section 9.7, market access is granted based on the proof of reasonable safety only through the humanitarian device exemption (HDE) Procedure. Nevertheless, the vast majority of medical devices obtain market access through the less stringent pre-market notification procedure, also referred to as 510(k) procedure, in accordance to the section of the United States Code ruling this market access route.

5.5 Postmarket Surveillance

In both legislations, manufacturers have postmarket adverse event reporting and vigilance requirements.

In the EU serious adverse events have to be reported within a ruled timeframe to the competent authority of a member state. Subsequently, they have to conduct their own risk assessment and take appropriate regulatory action. The outcome of the risk-analysis will then lead to recommending measures and corrective action to be taken as well as withdrawal of market access or restriction of supply.

6 Clinical Evidence Building for Medical Devices

6.1 The Development Process of Medical Devices

In comparison to drugs, medical devices are an extremely heterogeneous group of products. They are not based on scientific discovery, like drugs are, but invented and developed instead. The innovation and product development process of medical devices and the underlying technical expertise differ in some significant ways from the process of invention of a new drug [28]. In this process, a physician often participates in a key role. He may start-of the development of a new medical device in delivering the specifications of unmet therapeutic needs and comprehensive clinical insight with regard to the suitability (human factors, environment) of a proposed technology [22]. The interaction between health care professionals and engineers can pave the way for a novel orphan product. The more sophisticated a multidisciplinary network works, the better informed take project decisions can be taken. The stages of clinical development can be distinguished into an exploratory (first-in-human/ pilot/ feasibility) and a confirmatory/ pivotal one. With the preliminary safety and performance data the

design of confirmatory clinical testing can be supported. Due to the mode of operation of medical devices contrasting from drugs, the functions operating on physical properties are clinically tested with regard to performance according to specifications in order to demonstrate compliance to the essential requirements. The conduct of well-controlled clinical trials may often not be feasible due to the nature of the device (i.e. implant) or because of ethical reasons. Therefore the rate of product turnover is relatively rapid due to short life cycles (1,5 – 4 years). This may have a negative impact on the long-term monitoring and evaluation of safety and effectiveness with regard to rare adverse events. In order to apply the appropriate level of testing and regulatory oversight to a specific medical device, it is allocated to one out of three (U.S.) or four (EU) risk-classes as elaborated in section 5.3.

For products classified as high risk devices incorporating of novel technologies (first-in-class) usually clinical studies need to be conducted in both regions, if essential requirements are identified that “require support from relevant clinical data” in the EU [53, 54]. With regard to establishing a favorable risk-benefit ratio a clinical trial may be necessary for collecting the data required supporting a PMA. Nevertheless, the requirements with regard to the nature and extent of clinical data diverge in the two regions. According to EU Medical Devices Directives, it is required to demonstrate that the device complies with the essential requirements as ruled in the Annexes I of the EU Directives. It is required to demonstrate that the device is safe functions as intended by the manufacturer. The manufacturer is responsible for setting the specifications with regard to an acceptable level of safety and specifying the performance criteria. The development process methodology applied to a medical device therefore is crucial with regard to iterative steps for risk mitigation and performance qualification. Incremental technical improvement steps are integral part of a process involving experts from multiple disciplines. The conduct of a risk analysis including all expected hazards associated with the design in normal and failure condition, including use error. This is by contrast to the U.S.’ FDA requiring reasonable assurance of safety and “proof of effectiveness“. The regulatory approval threshold is defined by FDA through the enacted federal regulations and specified by guidance documents and not by the manufacturer, as it is the case in the EU. The product development process is aiming at are closely linked the regulation governing market access. Emerging technologies enable the development of novel, sophisticated medical devices with features posing high risks to human subjects in case of malfunctioning, misuse or use

error. Among these there are drug/ device combination products, medical devices containing nanomaterials or implantable drug delivery devices, just to name a few. Due to the probable impact of the specific features of any “cutting-edge” technology, the risks associated with these healthcare products cause are not well understood in the beginning of use and therefore associated with a high degree of uncertainty. The innovation process for medical devices is often incremental and involving ongoing product modifications and improvements. Accordingly the rate of product turnover is rather rapid. Therefore data of a specific device type may remain limited and cannot be aggregated with data generated with new types.

6.2 Conditions for Market Access

6.2.1 Evidence of Safety

Several regulatory systems require the manufacturers to demonstrate the safety of the medical device in a premarket review process. There is an international consensus that the design of the device should be validated as a condition for market access. There are legislations that solely rely on establishing safety, others understand safety in conjunction with proof of effectiveness [44]. A device is considered to be safe, if the benefit outweighs the residual risks, which are valued as acceptable by the manufacturer in the EU, and contrastingly assessed by the FDA. A risk is defined as combination of the severity of harm with the frequency of occurrence of it. The acceptability of a risk level is estimated by the manufacturer’s own policy, taking into consideration similar medical devices and state-of-the-art performances.

“FDA’s statute and regulations do not define “safe” or “safety” as such, but describe criteria for determining that a medical product is safe: „there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks” (21 CFR 860.7 (d)(1)).

EU Directive 93/42/EEC states „Whereas medical devices should provide patients, users and third parties with a high level of protection and attain the performance levels, attributed to them by the manufacturer; whereas, therefore, the maintenance or improvement of the level of protection attained in the Member States is one of the essential objectives of this Directive“ .

6.2.2 Establishment of a Risk Management Process

The EU manufacturer is required to mitigate unacceptable risks through design, alarm or instructions for use. It is to a manufacturer's discretion to decide about the level of acceptable risks according to the harmonized standard DIN EN ISO 14971:2012. The risk analysis has to be updated in case new relevant safety data arise.

The FDA suggested two tools for the conduct of risk analyzes [23, 55]:

- Failure mode and effects analysis;
- Fault tree analysis.

In the risk analysis any potential anticipated hazard to human use has to be identified, based on experience, literature research and preclinical testing, considering state-of-the-art technical knowledge and are weighed against the probable benefits to patients in a comprehensive manner and sufficient detail to support the conclusion that the risks to the patients are not unreasonable. The risk analysis reflects a consideration of potential failure modes, the measures to mitigate the corresponding risks in order to minimize overall risk as low as reasonable possible.

6.3 Performance

According to Guidance MEDDEV 2.7.1 Rev.3 [53] on Clinical Evaluation, "Performance is the ability of a medical device to achieve its intended purpose as claimed by the manufacturer" [31] and in accordance with associated labeling technical specifications of relevant product standards. [44]

6.4 Effectiveness

6.4.1 Definition of Effectiveness

"Effectiveness" means a product can be shown by valid scientific evidence to produce an intended clinical effect in a target population." (WHO 2009) [43].

6.4.2 Evidence Requirements

The manufacturer is required to demonstrate to the FDA through valid scientific evidence the „reasonable assurance of safety and effectiveness“ by „weighing any probable benefit to health from the use of the device against any probable risk of injury or illness from such use,...“. According to Section 513(a) FD&C Act the FDA is authorized to determine about the reasonability of assurance [20, 56].

Regarding the overall impact of a regulatory go/no go decision it is essential to clarify the nature of the data set on which it is based. The FDA frequently uses the term “valid scientific evidence” and clearly states what data are considered under these terms: “Valid scientific evidence is defined as “evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device”, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use.” [20].

In the EU, there is no legal requirement regarding evidence of patient-relevant clinical benefit, but the manufacturer demonstrates conformance with the essential requirements with regard to safety and performance, based on a risk analysis and in weighing the residual risks against intended benefit to patients. The EU conformity assessment procedure does not necessarily rely on effectiveness data and therefore the exemption from a requirement to demonstrate “reasonable assurance of effectiveness” can probably not have appropriate impact as an incentive for orphan devices in the EU. In the EU, “there is no requirement to assess short- and long-term harms in well-designed RCTs, with the use of blinding and hard end points whenever possible.” [58]. The EU data requirements for premarket evaluation are not strongly related to the demonstration of effectiveness or patient relevant benefit [58].

6.5 Risk Benefit Evaluation

A riskless medical device does probably not exist. Minimal risk devices may be accepted only, if there is a high degree of uncertainty regarding anticipated benefits. Some regulatory experts are of the opinion that „device safety is inextricably linked to effectiveness/performance“. The risk level in the context of life threatening or chronically debilitating unmet medical needs may be accepted even if it is high and/or uncertain [44]. Therefore, a well-informed decision may be taken regarding the risks of a medical device if weight against benefits that are relevant to the patient and that have been demonstrated. A “reasonable assurance of safety and effectiveness” is determined by the FDA under section 513(a) of the FD&C Act in “weighing any probable benefit to health for the use of the device against any probable risk of injury or illness from such use”, among other relevant factors.” It has to be demonstrated, based on valid scientific evidence, “the absence of unreasonable risk of illness or

injury associated with the use of the device for its intended uses and conditions of use” in the meaning of 21 CFR Part 860.7(d)(1) [59, 60].

7 Challenges of the Orphan Medical Device premarket Clinical Development

7.1 Universal Challenges of Medical Device Clinical Development

For the purpose of establishing best clinical practice there should be made no difference between the drugs and medical devices. In any case valid scientific data are essential for establishing evidence-based therapies and guidelines for clinical services in the long run. The process of translation of experimental use of a drug or medical device into evidence based medical practice usually is not completed for medical devices when market access is granted in any legislation.

The input of physicians to the development process assumes a high level of medical expertise with regard to the rare disease that is targeted with the device. Therefore the “centers of expertise” concept supports best practice in rare disease healthcare. The established models for the clinical development of drugs are not fitted with medical devices. Their distinction of premarket clinical development phases I, II and III takes account for the unknown pharmacological and pharmacokinetic effects, which, by contrast, are not present in medical devices. For medical devices the mode of action has been designed and has been verified by in preclinical performance testing [61]. Therefore, only two fundamental phases can be described in the premarket clinical development of medical devices

- An exploratory phase including first in human and feasibility clinical trials, aiming at generation of safety and preliminary performance/ effectiveness data.
- A confirmatory phase with regard to pivotal performance/effectiveness data supporting premarket assessment applications.

Regarding the validation of performance, there is a vast acceptance of surrogate endpoints like „isolation of the vein“ of an ablation device in arrhythmic cardiovascular diseases, for example.

The learning curve often has to be taken into account and usability is impacting performance. Furthermore, problems may arise far from the original place or time a de-

vice was used or implanted, for example, in the home or under the care of a physician not associated directly with the device. Adding to the complexities of device research per se are the technical complexities of conducting pediatric studies including small populations and special research protection regulations.

Medical devices differ from drugs in many regards:

- Medical devices are a very heterogeneous group of products with different features and a wide scope of technologies incorporated.
- Medical devices have a very short life cycle due to vast emergence of new technologies or technical features.
- The physical mechanism of action of medical devices can have local effects that are well measurable effects on physiology or histology of the human body or otherwise interfere physically with the human body in a way, that may not be well understood (e.g. stimulating the nervous system).
- With medical implants, exposure to the product is not terminated and associated with irreversible consequences to patients.
- Sources for „valid scientific evidence can come from other than well controlled trials (e.g. uncontrolled trials, historical controls).
- The regulatory rigor of the requirement to demonstrate reasonable assurance of clinical effectiveness (US) or performance (EU) is more moderate for medical devices and no replication of clinical findings is required but only one pivotal clinical trial (US) or a clinical evaluation (EU) that may be based on data derived from clinical trials and/or historical data.
- Medical devices are designated an intended use by the manufacturer that is reflected in the risk analysis and revealed in the investigator’s brochure or the instructions for use.
- The performance of medical devices often is often linked to user’s skills, who often is a specialized physician.
- The use of the medical device frequently is embedded into a medical procedure that is linked to the performance of the device and may have an influence over the overall risks presented to the patient.
- The risks associated with the use of medical devices may vary with a physician’s judgment.

- Medical devices are not discovered but developed and usually have short life-cycles due to often incremental technical advancements.

Medtech companies are often small which sets limits to the nature of development and testing since per-product revenues are relatively small compared to drugs.

These differences of medical devices require adequate phasing of clinical trials during the clinical development, differing from those for drugs. Well-controlled studies are often not feasible e.g. owing the fact that the user cannot be blinded to the study intervention or may be precluded due to ethical considerations (sham-procedure unethical). Moreover, the results from long-term clinical studies may no longer be relevant to modified products and varied medical procedures that have an impact on the outcome.

Medically appropriate alternative treatment regimens may not be available to provide randomized, concurrent controls. Long-term performance evaluations of implants primarily rely on design controls and failure analysis, which may be based on registries designed with appropriate methodology.

7.2 Challenges in the Development of “Orphan Devices”

7.2.1 Small Patient Population

Due to small number of patients, multi-center clinical trials are needed in order to have adequate power. International cooperation can assist in aggregating participants into one clinical trial.

7.2.2 Centers of Expertise

The etiologies of diseases are often unknown unless there are physicians who dedicate their career to any of these, accepting to remaining studying it for many years. They can only act in close co-operation with their patients and their families. There often is no medical society existent that is elaborating standards of treatment and supporting clinical decision-making. A physician has to be deeply committed to his patients and cannot approach his patients from a position of know-it-all doctor. Rare diseases are often more complex than common diseases and therefore the pathophysiology seldom understood [62]. Therefore, in the EU rare diseases policy centers of expertise are part of the strategic concept.

7.2.3 Research Consortia

The International Rare Disease Research Consortium (IRDiRC) was launched in April 2011 to foster international collaboration in rare diseases research. The European Commission and the US National Institutes of Health initiated the discussions, and other stakeholders, including other funding agencies, have also been invited to join the consortium. IRDiRC will team up researchers and funding agencies in order to achieve two main objectives by the year 2020, namely to deliver 200 new therapies for rare diseases and diagnostic tools for most rare diseases [15].

8 EU Premarket Assessment Procedures for Medical Devices

8.1 Legal Framework

The systematic EU regulation on medical devices is more recent than the pharmaceutical legislation and was enacted during the 1990s. Medical devices regulated within a supranational legislative concept originally designed for technical goods and referred to as the “New Approach”. This is due to the nature of the EU, functioning is an organization governing 28 independent European member states. With regard to medical devices, each Member State has transferred the authority to enact laws to the EU government aiming at harmonized rules for a single EU market. The framework of this New Approach aims to protect public health in setting high levels of safety and to provide access to the Community market and at the same time promote innovation and technical harmonization. In principle, this is reached by demonstrating compliance to the essential requirements when following the provisions of applicable. In an effort to harmonize the requirements for medical devices, three core directives have been enacted, outlining the supranational regulatory mechanisms until today, but leaving the implementation into each member state’s national law through a national obligation to transpose the EU legislation [62, 64, 65]:

- Directive 90/385/EEC covering implantable medical devices (AIMDD)
- Directive 93/42/EEC ruling medical devices that are not within the scope of any other directive (MDD)
- Directive 98/79/EC concerning in vitro diagnostics (IVDD)

The directives have been amended several times, taking into account the vast technical innovation and internationalization of the market, and particularly in 2007 by Directive 2007/47/EC [3].

This legislation is aiming to ensure a high level of protection of human public health and their safety. They also enable a single EU market for medical devices in overcoming barriers with regard to national requirements of technical specifications (use of standards as outlined in section 8.4. Taking into account the vast technological progress and global harmonization, the directives have been amended with regard to the requirement of clinical data forming the basis for clinical evaluation. Other current issues are the definition of software functioning as a medical device, coordination of efforts within the EU Member States and the public's expectations regarding transparency. The advent of some drug/device combination products required the establishment of procedures for evaluation of the drug. The Guidance MDDEVs complement the EU directives in the effort to promoting "a common approach by manufacturers and Notified Bodies involved in the conformity assessment procedures according to the relevant annexes of the Directives, and by the Competent Authorities charged with safeguarding Public Health" and to establish harmonized procedures [4, 29].

8.2 Manufacturer's Responsibility

The manufacturer's responsibilities are outstandingly high in the EU legislation. Many activities with pharmaceuticals require prior approval of a competent authority [8]. By contrast to pharmaceutical products, medical device regulation is based on the conformity to legal essential requirements. Compliance has to be demonstrated by the manufacturer prior to placing a product onto the market. The onus of ensuring and declaring conformity is therefore placed on the manufacturer.

8.3 Essential Requirements

The essential requirements as laid down in in Annex I to the Directives 93/42/EEC and 90/385/EEC, relate to the safety in the use of the device and comprise labeling requirements. They are expressed in terms of scientific and technical performance characteristics. Efficacy is not implemented into the essential requirements [4]. They are arranged into two sections:

1. General Requirements.

2. Requirements regarding design and construction.

The essential requirements state the overall requirements for suitability of technical design related to the risk-benefit equation in the purpose intended by the manufacturer and comprise labeling requirements. They are generally expressed in terms of scientific and technical performance characteristics. Efficacy is not reflected in the essential requirements [2, 8].

The purpose is to define a harmonized scope of requirements that have to be met. They are a crucial component of the “New approach” concept of EU Council of 1985 regarding technical devices [16, 18].

8.4 Use of Standards

EU harmonized standards are a core element of the “New Approach” concept, and are utilized to ensure presumption of conformity to the essential requirements with regard to technical specifications. Therefore, the harmonized standards function as a means to define harmonized technical specifications of medical devices for the single EU market, for which they constitute a prerequisite. The scope of harmonized standards can be focused on one single group of medical devices (e.g. cardiac pacemakers). Otherwise they may address one aspect relevant to any medical device and applicable in conjunction to “vertical” standards summarize best practice [20, 21]. Three examples of “horizontal” harmonized standards are:

- DIN EN ISO 13485:2012 requirements for the total quality management system in accordance with the three medical device directives.
- DIN EN ISO 14971:2012 outlining the fundamentals of risk management methodology.
- DIN EN ISO 10993-x series specifying biocompatibility test requirements.

The development of standards is fostered by national private non-profit organizations through committees consisting of all industry, public authorities and research organizations. Yet the access to standards is associated with costs, due to the limitation that only private publisher are authorized to sell them and restrict their use to single working units [21]. The application of standards bears the concept of extensive regulatory adaptability to evolving technologies [19].

8.5 Premarket Conformity Assessment Procedures

In the EU's conformity assessment procedures according to annexes II-V of the directives applicable for class III medical devices, the manufacturer has to demonstrate that the medical device has been designed, is manufactured and will be distributed according to a full quality management system (QS) that conforms to the applicable essential requirements of the directives. The presumption of conformity to annex II of the directives can be established in evaluation of a full quality system according to DIN EN ISO 13485. The risk management process is a core feature in the QS, aiming at control and assessment of the residual risks.

The clinical evaluation is one crucial element of the conformity assessment procedure in terms of whether it is established by the manufacturer that the anticipated clinical benefits remain favorable when weighed against the residual risks resulting from a risk management process as outlined in the standard DIN EN ISO 14971. A clinical evaluation is defined in the Guidance MEDDEV 2.7/4 (Dec. 2010) [26] as an "assessment and analysis of clinical data pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer". The Directive 2007/47/EC, amending the MDD and AIMD, specifies clinical data requirements regarding their source and validity. The manufacturer's clinical evaluation report became mandatory for the conformity assessment [30]. The clinical data are to be presented within a clinical evaluation report, which now is a mandatory component of the technical file. The standard DIN EN ISO 14155:2011 sets out the framework for good clinical practice for the design, conduct, data management and reporting of clinical investigations carried out in humans with the purpose of assessing the safety and performance of medical devices for regulatory purposes. If a device incorporates novel technologies or materials or was ascribed a new intended use, appropriate and specific requirements to for presumption of conformity should be set out in an applicable standard. If an essentially similar device existed, historical data may complement the clinical evaluation adding to data derived from clinical trials with the new medical device or may from the only basis for the clinical evaluation. Unless a product specific harmonized European standard requires a comparative clinical trial establishing effectiveness, the general requirement of clinical evaluation can be satisfied without the conduct of a well-controlled clinical trial. Even in case the applicable standard would state otherwise, the manufacturer can deviate from it if justified. The sponsor's responsibility cannot be underestimated. Therefore, in theory,

it is possible that apart from a product-specific recommendation for comparative effectiveness trials, an innovative medical device may enter the market if the manufacturer's justification for deviating from the standard is accepted by the notified body.

8.6 Notified Bodies

There is no centralized European agency mandated for the premarket assessment of medical devices. One of the tasks of the European Commission is to provide for regulatory guidance, promote harmonization among member states. The Commission is significantly participating in creating European medical device legislation. Nevertheless, the regulatory responsibility rests with the 27 Member States (MS) of which each has its "own national competent authority" [32]. Each competent authority can appoint one or more notified bodies (NB) by accreditation to execute duties outlined in the directives. Approximately 70 NBs of varying expertise currently work in the EU and are delegated the responsibility for overseeing the pre-market-assessment procedure of medical devices. NBs are independent technical and for-profit organizations competing with each other for manufacturers as customers and are monitored by domestic competent authorities.

8.7 Manufacturer's responsibilities

Many activities with pharmaceuticals require prior approval of a competent authority. The regulatory systems for medical devices are quite different from those for pharmaceuticals. The conformity to legal essential requirements has to be demonstrated by the manufacturer before placing a product onto the market and therefore the onus of ensuring and declaring this is placed on the manufacturer.

8.8 EC Certificate of Conformity

The manufacturer has to certify the conformity by completing a declaration of conformity. In general, the manufacturer can choose between two main approaches to conformity assessment. It can be based either on an individual product assessment or on an approved total quality management system audited to Din EN ISO 13485:2012.

Regulatory essential requirements relate to the safety for patient and user. They are regarded in relation to the intended performance claimed by the manufacturer and recognized through the essential requirements. They relate to the safety in the use of the device as intended and comprise labeling requirements. They are generally ex-

pressed in terms of scientific and technical performance characteristics. Efficacy is not reflected in the essential requirements.

8.9 CE Marking

The conformity of a medical device to the essential requirements is indicated by affixing a CE marking to the device. When the CE marking is affixed, this represents a declaration by the person responsible, that it conforms to all applicable Community legislation and that appropriate assessment procedures have been successfully completed. CE refers to Conformité Europeene and acts like a passport that allows the device to be placed onto the EU single market.

8.10 Outlines of the Proposal for a New Medical Device Regulation (MDR)

Revisions are expected to the medical devices regulation reflecting amendments to the „new approach“ legislation according to the Proposal of the EU Commission for a regulation on medical devices, active implantable medical devices and in vitro diagnostics:

- Regulation (EC) No 178/2002
- Regulation (EC) No 1223/2009

In general, the current system has operated well for two decades since its enactment. It has promoted a single European market while protecting human health. Yet the risk to patients from medical devices to patients is to be controlled sufficiently with regard to emerging complex novel devices. The novel EU Medical Device Regulation is expected to enter into force by 2016. One key issue will be the scrutiny procedure for significant risk medical devices (scrutiny procedure).

8.11 Implications for Orphan Devices

There is no designation for orphan devices in the EU.

The threshold for CE-mark approval does not offer any flexibility with regard to classification of the condition or population in which it risks to human use are judged to be acceptable based on the risk analysis and comprehensive data demonstrating technical safety and acceptable level of biocompatibility and performance as intended by the manufacturer when weighed against the anticipated benefit.

9 U.S. Premarket Procedures for Significant Risk Medical Devices

9.1 Legal Framework

The U.S. regulation of medical devices is governed, along with drugs and other products, under the Federal Food, Drug, and Cosmetic Act of 1938 (FD&C Act), as amended (P. L. No. 75-717, 52 Stat. 1040 (1938)) [14, 37]. The Center for Devices and Radiological Health (CDRH) at the Food and Drug Administration (FDA) was charged with ensuring the safety and effectiveness of medical devices. The act originally exclusively covered legally marketed devices that were sanctioned to be unsafe or misbranded, but did not authorize the FDA for premarket assessment.

9.1.1 The Medical Device Amendments of 1976

Until 1976, US federal government had very limited authority to govern the safety of effectiveness of medical devices. With the implementation of the Medical Device Amendments (MDA) of 1976 (P. L. 94-295), the increasing complexity and relevance of medical device technology was acknowledged and the present day medical device regulatory framework was founded. The FDA was empowered with the authority to regulate safety and clinical effectiveness. Clarification was provided about the definition of medical devices by their contrasts to drugs. At the same time it was recognized that a systematic concept was warranted to draw FDA's attention to the premarket assessment of safety and efficacy benefits of the medical devices and establish a mechanism for premarket approval or notification, depending on the product's inherent risks to human use. Recognizing the diversity of medical devices, they were allocated to one of three risk classes (I, II or III) in order to apply the appropriate regulatory oversight to them. This concept was explained in section 5.3.

Nevertheless, the newly enacted premarket assessment mechanisms did not apply to medical devices that were legally marketed before the enactment of the MDA in 1976. Therefore they continued to be marketed as so called "predicate" or "pre-amendment" devices that divided the market into two sections. Moreover, if "essential similarity" can be established in relation to a "pre-amendment" device in consideration of the intended use and device technology, for these post amendment devices the mandate for a premarket authorization, based on demonstration of safety and effectiveness, does not apply. For the first time, FDA was authorized to describe good manufacturing practices.

9.1.2 The Safe Medical Devices Act of 1990

The FDA's authority was strengthened regarding the regulation of safety and clinical effectiveness of medical devices in order to carry out their mandate to protect public health through the Safe Medical Devices Act of 1990 (P. L. 101-629). It required facilities that were using medical devices to report serious incidences related to patients' health. Postmarket surveillance was strengthened for high risk devices. The FDA was authorized to recall hazardous medical devices. The rules and authorities in the classification process were varied. Moreover, regarding medical devices with intended use in diseases and conditions that affecting less than 4,000 individuals in the United States, section 520 of the FD&C Act was amended by the "Humanitarian Device Exemption" [3, 38-40]. The purpose was to foster the development and patient access of medical devices intended for such small populations.

9.1.3 The FDA Modernization Act of 1997

With the enactment of the FDA Modernization Act of 1997 (P. L. 105-115), some provisions of the 1990 legislation were updated concerning adverse event reporting and mandatory postmarket surveillance studies that may be ordered by the FDA along with the premarket approval. In addition, more FDA resources were authorized on the administration of significant risk device regulation. The requirements for the protection of clinical trial participants were enhanced including special protections for children [66].

9.1.4 Medical Device User Fee and Modernization Act of 2002

With the Medical Device User Fee and Modernization Act of 2002 (P. L. 107-250), the regulatory procedures for medical devices were streamlined.

In addition, provisions were included for pediatric use of the devices. One is the obligation to report on postmarket surveillance on medical devices used in pediatric populations.

9.1.5 The Pediatric Medical Device Safety and Improvement Act of 2007

The Pediatric Medical Device Safety and Improvement Act of 2007 (P. L. 110-85) addressed the shortfalls in the development of pediatric medical devices. It mandated a tracking system of pediatric device approvals by the FDA for the first time. It also included two provisions stimulating pediatric device development:

Elimination of the profit restriction on pediatric devices approved under the HDE pathway, authorization of appropriations for grants to non-profit consortia for projects that demonstrated to promote pediatric device development [65].

9.2 Medical Device Panels and Advisory Committees

The expertise of FDA's CDRH is supplemented by external expertise in order to carry out its regulatory decision-making. The collaboration with healthcare professionals practicing in a specific therapeutic area is formalized through the advisory committee system, comprising 18 panels relating to medical areas i.e. circulatory system devices or neurological devices for example.

9.3 Use of Standards and Guidance

FDA's CDRH Standards Management Staff ensures adequate medical device standards are published in the Federal Register as the last step of a formalized process that was created as a result of the FDA Modernization Act of 1997 [44]. The applicant may provide documentation to establish conformance with applicable standards. In addition, FDA guidance documents with relevance to the safety or effectiveness of a device should be provided according to 21 CFR Part 814.20(b)(5). In the U.S., the FDA is authorized to recognize voluntary standards of which many have been developed with the participation of CDRH staff. Conformance with a recognized consensus standard can support the premarket evaluation requirement to demonstrate reasonable assurance of safety and effectiveness with regard to many aspects for significant risk devices going through the PMA procedure. In case of conformance in a premarket notification, this may bridge the establishment of substantial equivalence, therewith allowing for market access through the notification route 510(k). As a declaration of conformity to a standard is accepted by the FDA and the requirements for submission of test data will be eliminated for the aspects covered by the standard. Instead, FDA is authorized to inspect and audit underlying test data to confirm conformance as declared by the manufacturer [23-25].

9.4 Premarket Notification Procedure (510(k))

Class III medical devices are exempt from premarket approval if FDA finds them to be "substantially equivalent" to another exempt device. The determination of "substantial equivalence" is based on § 510(k) of the FD&C Act. In the "510(k) procedure"

the manufacturer notifies to the FDA to which devices he is claiming substantial equivalence, based on the characteristics of materials and intended use [7, 68].

9.5 Investigational Device Exemption (IDE)

Prior to the conduct of a clinical study with an unapproved medical device investigational exemption (IDE) approval according to 21 CFR 812 is required. The purpose of the study is limited to the collection of safety and effectiveness data in support of a premarket approval (PMA) or, in exceptional cases, in support of a 510(k) application. A modified medical device or a different intended use may require an IDE [9].

9.6 Premarket Approval Procedure (PMA)

The premarket approval procedure (PMA) according to 21 CFR Part 814 is mandatory for placing onto the market novel high risk devices without established essential similarity to a predicate medical device, prerequisite for the 510(k) route to market. If a medical device fails in the PMA and the application is denied, it cannot be marketed under section 501(f) of the FD&C Act. The PMA is the process “of scientific and regulatory review to evaluate the safety and effectiveness of class III medical devices” [20, 68]. Due to potential serious risks associated with the medical device, FDA has determined that general and special controls are not sufficient for these devices in order to provide assurance of safety and effectiveness.

The FDA determines if the application contains sufficient robust clinical data derived from one or more clinical trials or valid scientific evidence from other sources to demonstrate that the medical device is reasonably safe and effective for its intended use. For novel and more complex medical devices incorporating new technologies or ancillary drugs forming a drug/device combination product, an automatic class III designation is ruled. Unless they can be down classified through the de novo classification procedure initiated by the FDA or the manufacturer, they are mandatory for a rigorous premarket assessment within a PMA procedure. It is the most stringent premarket procedure through which went only 2% of all new medical devices for which an essential similarity to a predicate device has not been established. “FDA regulations provide 180 days to review the PMA and make a determination. In reality, the review time is normally longer.” The transparency of the procedure outcome is high due to publishing a notice in the internet including the data on which FDA’s decision is based. “The public has the opportunity to petition FDA within 30 days for reconsidering the decision” [68].

9.7 Non Standard Approval Route for Small Populations

The regulatory requirements for high-risk devices should not impede technical and medical progress, but be appropriate and encouraging for the development of medical devices, even for rare diseases. In this spirit, a non-standard premarket program was enacted by U.S. Congress with the Safe Medical Devices Act of 1990 (P. L. 101-629). The Humanitarian Use Device (HUD)/ Humanitarian Device Exemption (HDE) concept was implemented as a two-step process. The alternate approval route is only eligible for medical devices that are designated as HUD.

This exemption was implemented in order to provide incentives for development of medical devices for small populations [38, 44].

9.7.1 The Humanitarian Use Designation (HUD)

On request to the Office of Orphan Products (OOPD) [46, 47] a manufacturer may be granted a humanitarian use designation according to 21 CFR Part 814 Subpart H [69]. As ruled in 21 CFR Part 814.3(n), “an Humanitarian Use Device (HUD) is a medical device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year.” [5].

The Statutory Conditions for granting a designation are:

- The rare population criterion specifies that “medical device is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year” (21 CFR Part 814.102(a)(5).
- The Sponsor must periodically report data to the CDRH to demonstrate the continued appropriateness of the HUD designation.
- The medical device addresses an unmet medical need, that is life-threatening or seriously debilitating and CDRH will not approve a HDE if a comparable device has been cleared or approved for the same indication through either the 510(k) notification process or PMA approval process [47, 48].

9.7.2 The Humanitarian Device Exemption (HDE)

In order to provide a specific pathway for humanitarian use devices (HUDs) to support timely market entry, U.S. Congress created a non- standard premarket approval

procedure, the humanitarian device exemption (HDE) procedure (21 CFR Part 814 subpart H). Approval authorizes marketing of a HUD under the condition of individual and continuous IRB approval. The PMA can be streamlined due to the HUD designation program in the Office of Orphan Products Development (OOPD).

9.7.2.1 Data Requirements

The manufacturer has to demonstrate,

- that the device does not pose unreasonable risk of harm,
- the probable benefits outweigh the risk of harm.

The medical device is therefore exempt from the requirement to demonstrate reasonable assurance of effectiveness.

To encourage development of medical devices for rare diseases, the approval threshold has been lowered concerning effectiveness data requirements and is met if the applicant demonstrates that the device is safe and can establish the expectation of probable benefit to patients [72, 73].

9.7.2.2 Incentives

FDA intends to encourage manufacturers to interact with the agency in order to develop an appropriate approach specific to the needs of the devices [13, 49].

- Tax reduction of development costs.
- The non- standard requirement of lower level of premarket clinical evidence due to exemption from the requirement to demonstrate, reasonable assurance of effectiveness.
- The filing fees are waived.
- The time lines for review are shorter than for PMAs.
- Manufacturers are eligible for orphan products grants.

9.7.2.3 Statutory Conditions for Use of HDE

The use of humanitarian device exemptions is associated with burdens to the healthcare professionals, the healthcare settings and the manufacturer. Due to the exemption from the requirement to demonstrate reasonable effectiveness, tight controls for use are implemented. The use of the humanitarian device exemptions is considered non experimental if used according the terms of approval. Nevertheless, the IRB is authorized to approve the use beyond the approved intended use.

The approval of a local institutional review board (IRB) is required for each single use of the medical device,

In an emergency situation, when a physician determines that approval from a local IRB cannot be obtained timely, the device may be used and IRB has to be notified if, before the use of a device, an institutional review committee approves the use in the treatment or diagnosis of a disease or condition referred to in paragraph (2)(A), unless a physician determines in an emergency situation that approval from a local institutional review committee cannot be obtained in time to prevent serious harm or death to a patient.

Revenues to the manufacturer used to be not allowed, until this statutory condition was varied twice; first regarding pediatric medical devices and then all patients.

Shipment records and distribution numbers have to be reported by the manufacturer periodically.

The labeling has to include the statement according to 21 CFR Part 814.20(b)(10) and 21 CFR 814.104(c)(4)(ii): "Humanitarian Device".

9.7.2.4 HDE in Regulatory Practice

The Draft Guidance on "Humanitarian Device Exemption (HDE): Questions and Answers " was issued in March 2014 [74] in order to provide clarity about practical aspects of the procedure and the post approval requirements:

- The extent of use of a HDE is controlled through the manufacturer's reports on shipment.
- The scope of IRBs is has not sufficiently been clarified, as they generally are reviewing investigation plans and documents associated with biomedical research.
- The use of a HDE is not considered research unless data are collected from off-label use according to a protocol or not; In this case an informed consent procedure has to be followed; Nevertheless, an IDE is not required, since the HDE is already on the market.

The HDE provision does not include provisions for market exclusivity.

The manufacturers' own experiences as retrieved in literature [31, 74, 76]:

The most effective incentive is probably the exemption from the requirement to demonstrate reasonable assurance of effectiveness due to the high costs and time consuming clinical trials, that otherwise would have to be conducted in support of the effectiveness claim.

Because of the time saving opportunity to access the market earlier, some of the research and development costs may be partially recovered and enable the manufacturer to proceed with a premarket application. The authorized medical device may then benefit from protection against competitors due to the humanitarian use device and despite of unlimited market access.

„The HDE process is generally viewed as confusing and burdensome. FDA could act, within existing law, to make the process less intimidating and potentially more attractive to device developers“. Accordingly, recommendations were made by the expert group to provide for clarification of the sponsor’s duties relating to Humanitarian Use Devices with regard to [77]:

- Industry recommends to assign an ombudsman to help sponsors navigate the regulatory process.
- The provision of specific guidance and technical assistance on the documentation required for the designation with regard to sample size is crucial.
- There may be more than one HUD available with the same intended purpose.
- Post approval safety reporting requirements as the reporting of serious adverse events (deaths, life-threatening or debilitating outcomes).
- The approval of a local IRB is causing relevant additional administrative burden and therefore generates costs.

In conclusion, the HUD/ HDE concept bears a favorable and necessary paradigm change for regulation of medical devices due to the expansion of legislation beyond protecting patients from unsafe and ineffective medical devices and to impact and promote the market access of a predefined category of medical devices. It can be argued, that there is potential for improvement of the concept concerning the impact factors and criteria for a streamlined market access. The conclusion is based on the papers quoted above, the case studies elaborated in section 9.7.3 and on two comprehensive publications of the U.S.’ Institute of Medicine focusing, among other top-

ics, on unmet medical device needs in rare diseases in consideration of pediatric patients [78] [66].

The support for medical device innovation in the area of regulation is an effective element of promotion, but should be comprehended by others like research funding or market exclusivity grants. Nevertheless, it can be concluded that the data requirements for market access have the highest impact on a company's decision and ability to pursue product development due to the high costs of clinical validation and the uncertainties associated.

The borderline between experimental and non- experimental use of HDEs is crucial and the informed consent principle in case of experimental use has to be followed.

The requirements to generate clinical data in standard practical care are not a statutory condition for all HDE's, although the clinical data may in aggregate form the basis for the proof of effectiveness or disprove anticipated benefit.

“The threshold that innovations cross to reach the market sets in place an important foundation. This foundation must be established on the basis of good scientific principles and data to have its intended impact benefit to the public health without undue delay” [78]. Nevertheless, market access is one time point within a medical device's live cycle and data collection should continue because after market entry to clinical use, safety concerns may emerge that were not evident in clinical testing.

9.7.3 Case Studies of HDEs

9.7.3.1 *Wingspan Intracranial Stent (Neurology)*

The Wingspan Stent System, manufactured by Stryker, is a neurological medical device intended to widen the lumen of narrowed arteries of the brain due to intracranial stenosis, which is a serious condition due to risk of life-threatening strokes. The FDA approval as an HDE was in 2005 for the population with patients refractory to pharmacotherapy, which was by then standard medical treatment [80]. Later on, the labeling of the medical device system was changed in order to define a more specific patient population for intended use. This was due to new interpretation of the HDE clinical study and due to novel clinical data derived from a comparative clinical trial, the SAMMPRIS study [71, 81].

The clinical development of medical devices intended for the treatment of rare disease is a challenging task independent of the regulatory context it has been undertaken in. The case study of the wingspan device system points out the weaknesses of a regulatory system that is one of the few worldwide offering distinct regulatory pathways for humanitarian use devices. To what extent has safety to be demonstrated for an HDU or “orphan device” premarket? To what extent is the proof of efficacy feasible? In this case a pharmacotherapy has already been established as standard treatment. The wingspan device system is an implantable device targeting the brain and “is indicated for use in improving cerebral artery lumen diameter in patients with intracranial atherosclerotic disease refractory to medical therapy in intracranial vessels with $\geq 50\%$ stenosis that are accessible to the system.” [82]. Accordingly this therapeutic option inheres some constraints:

- Irreversibility due to implantation.
- The outcome is depending on the user’s skills.
- The eligibility criteria for patient selection need to aim at the greatest benefit possible in comparison to standard treatment.
- The therapeutic target is a vital organ system and the hazards associated with the use of the medical device potentially life threatening.
- The performance of the medical device has short term and long term characteristics and the clinical outcome is directly linked to the probable clinical outcome.

Subsequently to PMA approval, the long term performance evaluation was conducted with the means of a comparative clinical study (SAMMPRIS). Based an evaluation of clinical data from the HDE study and from the SAMMPRIS trial, the indication for use was narrowed as quoted:

„Wingspan is now approved only for patients who are between 22 and 80 years old AND who meet ALL of the following criteria:

- who have had two or more strokes despite aggressive medical management.
- who’s most recent stroke occurred more than seven days prior to planned treatment with Wingspan.
- who have 70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes and

- who have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is used to measure the degree of disability in stroke patients. Lower scores indicate less disability.

The Wingspan Stent System should not be used for:

- the treatment of stroke with an onset of symptoms within seven days or less of treatment; or
- the treatment of transient ischemic attacks (TIAs).” [10].

One eligibility criteria is the degree of atherosclerotic stenosis. This makes reference to relevance of state of the disease and underlying cause and the corresponding risks associated by natural disease progression as well as uncertainty about quick response to standard medical care. This case may demonstrate that the intended use of a medical device is crucial with regard to a favorable risk/ benefit ratio. In this case it would have been theoretically possible for the manufacturer to apply for a most narrow population and, as a next step and based on clinical and possibly additional pre-clinical data, to apply for a wider the population. The HDE/ HUD concept is designed exactly for such orphan devices as the small patient number is recognized as an impediment for market access for the manufacturer and the necessity to offer regulatory flexibility for such potentially life-saving therapeutic devices. In my opinion this case study demonstrates that, at the time of approval, the data were incomplete in relation to the indications for use. This case illustrates the relevance of the labeling and the necessity for adequate labeling requirements for HUD/ orphan devices.

9.7.3.2 *Excior Heart Support System (Pediatric Cardiology):*

Berlin Heart EXCOR Pediatric VAD is a pediatric medical devices with a design tailored to the needs of children in a life-threatening cardiologic condition. The pediatric device was designated as a HUD in 2001 and approved through a HDE in 2011 with intended purpose for use as a “mechanical circulatory support as a bridge to cardiac transplantation for pediatric patients. Pediatric candidates with severe isolated left ventricular or biventricular dysfunction who are candidates for cardiac transplant and require circulatory support may be treated.” [83]. The device assists the patient’s heart in supporting the weak ventricle to pump blood. The para corporeal, pulsatile cardiac assist system enables the patient to be discharged from the care unit into

their home setting, which is a contribution for a favorable clinical outcome e.g. survival until heart transplantation can take place or recovery is reached. Through the control technology, the system adapts to the needs of the child's activity. The pump volume is oriented on a change in blood pressure during physical stress. Upper and lower limits can be pre-set by the physician. The long absence of such mobile systems for pediatric patients led to complex and time relatively limited forms of therapy, such as the Extracorporeal Life Support Systems (ECLS or ECMO). The EXCOR Pediatric VAD is designed to support pediatric patients of all age groups, from newborns to teenagers, and can be used successfully for several months. By extending the duration of the cardiac support, more patients can expect a donor heart. According to the "Summary of Safety and Probable Benefit" of the HDE approval of EXCOR Pediatric VAD, EXCOR was CE-marked in the EU in 1996.

9.7.3.3 Deep Brain Stimulation (Neurology)

"The deep brain stimulation (DBS) system is an active implantable (EU AIMD) high risk (U.S. class III) medical device. The mode of action is to deliver electrical stimulation to specified physiological areas in the brain. The intended purpose is to target areas that are associated with neurological or psychiatric disorders. For specific subpopulations of chronic and drug refractory primary dystonia, the globus pallidus or subthalamic nucleus, the deep brain stimulation kit from Medtronic was authorized for market access under HDE conditions. The efficacy of this intended use has not been established and based on FDA's determination that the probable benefits to human health outweigh the risks of use within the terms of use conditions defined by the manufacturer and designated as a HUD, the medical device was approved under the HDE in 2003 [80]. The manufacturer Medtronic states on his homepage: "Surgery to implant DBS therapy for dystonia can only be performed in a medical center whose Institutional Review Board (IRB) has approved use of the device." [50]. This information is linked to the obligations of the HDE approval, which is considered market access, but under the condition of IRB approval for individual use or for use within one center. Therefore the market access may be considered as limited with regard to this obligation. Yet, the therapeutic option is not considered experimental, due to FDA's approval and if used under approved terms. IRB is authorized to specify the terms of use for which they give approval and may narrow the indication or expand into off-label use. In these cases, the use probably should be considered experimental. Gathering from the manufacturer's homepage, the listed indications as

movement disorders associated with Parkinson's disease, for example. There is information relating to a PMA for this indication, but information about use and success is demonstrated on the homepage, which is accessible also in the EU. It therefore can be concluded, that the approval through a HDE allows access to a medical device under approved conditions and beyond. The borders of experimental and non-experimental use are therefore clearly blurred. At the same time, there is no clarification or legislative obligation to collect clinical data, which is highly critical. Therefore it is crucial that the manufacturer informs about use in experienced centers, which may be interpreted as a recommendation.

“Despite the clinical success of DBS, the therapeutic mechanism of DBS remains under debate.“ [55]. New target areas in the brain seem to be infinite and treatment options continuously emerge for exploration.

“The history of DBS is a fascinating example of the interplay between basic and clinical research. It is the coming together of these 2 arenas that has led to the evolution of DBS for the treatment of disease as it is used today and will be used tomorrow.” [55].

The DBS technology bears numerous challenging features and aspects, not limited to medical and regulatory science. From a regulator's perspective the mode of action bears potential issues with regard to the uncertainty about overall effect cascade. The physical means may be the trigger for a complex neurological effect reaching far beyond what is considered a non-pharmacological, non-immunological, non-metabolic, non-chemical but physical effect. The dose-dependency and adjustability is a characteristic shared with drugs. Therefore, the DBS may be considered as a platform technology that accessed U.S. market with the exemption from the requirement to demonstrate reasonable assurance of effectiveness. The life-cycle of the platform technology will presumably exceed the average of a medical device of 1,5 – 4 years and in the long run clinical effectiveness data should contribute to the evidence building of this “last-resort therapy” [55]. Patient access to this implantable device is made possible through HDE without the prerequisite of the setting of a clinical investigation [67].

9.7.4 The Industry's Perspective on the HUD/ HDE Concept

The non-standard requirement of exemption from the requirement to demonstrate reasonable assurance of effectiveness in the HDE procedure is the most efficient incentive for the manufacturers to bring their product to the US market. This incentive implies an enormous financial value for the manufacturer who can bring his medical device to market 1,5 to 4 years earlier. Often the decision to choose the HDE pathway is made after IDE approval was granted and therefore in a very late development step. Summary of experiences with HUD/ HDE regulatory concept are quoted: „The HDE process is generally viewed as confusing and burdensome. FDA could act, within existing law, to make the process less intimidating and potentially more attractive to device developers“ [76]. Accordingly recommendations were made by an expert group to provide for clarification of the sponsor's duties relating to Humanitarian Use Devices with regard to:

- Assignment of an ombudsman to help sponsors navigate the regulatory process.
- Provision of specific guidance and technical assistance on the documentation required for the designation with regard to population size.
- IRB review of HDEs.
- Evaluation whether the medical device meets the needs of the identified patient population to meet the provision that no other medical device intended to treat or diagnose the specific condition should be available through a PMA. Yet there may be more than one HUD be available with the same intended purpose.
- Post approval safety reporting requirements as the reporting of serious adverse events (deaths, life-threatening or debilitating outcomes).
- Revenues / Profits for adult medical devices were not allowed until 1997. Pediatric medical devices were exempt from this provision. This is controlled by annual shipment reports the FDA. An attestation is required that the amount charged does not exceed the cost of research, development, fabrication and distribution.
- IRB Review is required initially and in addition continuously re-reviewed before the medical device is applied.
- The Risk-benefit assessment may be based on minimal data including anticipated benefit but on reasonable assurance of safety.
- Not exempt from the demonstration of reasonable safety in order not to compromise patient's safety.

- For pediatric medical devices scrutiny is applied to the oversight of adverse events for which closely meshed reporting obligations are specified, Since the “valley of death” can be surmounted by shortening the clinical development program due to the exemption from the proof of efficacy, industry may have the opportunity to create new market.
- Due to the FDA’s transparency in communication HUD-approvals and the provision of preclinical and clinical safety and anticipated benefit data, the effect on public relations is regarded as being “excellent” by some industry.
- The creation of value is demonstrated.
- It may be disadvantageous for the development of orphan combination products drug/ device that the incentives for orphan drugs internationally differ from orphan devices.
- Grants for pediatric medical devices may be provided as financial incentives for device development.
- A good working relationship with the FDA may be established.
- The FDA has the authority to require the sponsor to conduct longer postmarket oversight than the currently established standard of 36 months.
- Priority review voucher may be granted.
- The credibility with physicians is well established.
- Less effort is necessary to bring a product to the market which is critical for novel, disruptive technologies for which minimal data are necessary only.

9.8 FDA Guidance on Expedite Access

Regulatory systems/ frameworks for new medical devices should provide pathways to market access for promising innovations while equally ensuring patient protection from products with an unfavorable risk/ benefit balance. To achieve these aims, the United States and European Union apply a system that calls for a combination of sufficient premarket testing data and postmarket vigilance. Yet the details of the two approaches are vastly different. „Features of both environments require reform, as well as continuing research to assess policy changes.“ [30, 36]. In this context the FDA released two draft guidance documents in 2014 related to the expedited access for class III medical devices that are mandatory for PMA application [86]:

- Draft Guidance for Industry and FDA Staff (2014): Expedited Access for Pre-market Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions [36].
- Draft Guidance for Industry and FDA Staff (2014): Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval [37].

These two guidance documents provide for more flexibility in the FDA's premarket review process and complement the above outline recent regulatory tools, expedite review and a risk/ benefit methodology.

10 Discussion

10.1 Designation

Medical value in health care should not only be provided to patients with common diseases, but also to those afflicted by rare diseases. Usually, life science companies do not consider the smaller market segments attractive, fearing high costs vs. low investment yields. Among the overall development costs, the translational and clinical phases are the most expensive milestones during the entire development generating safety and effectiveness data. The most relevant proportion of the data correlates with the rigor applied during premarket evaluation of the regulatory context. The HUD/ HDE concept exempts promising novel devices from the requirement to demonstrate premarket effectiveness and accepts a favorable ratio of risk verses probable benefit instead. A medical device is eligible for the HDE procedure if it was designated as a HUD by the FDA'S Office of Orphan Product Development (OOPD).

This rule was created in order to relieve the manufacturer from some of the pre-market development cost burden. Through this regulatory mechanism, among others, the FDA seeks to accelerate the development of orphan devices, setting a very strong incentive. Taking into account the vast technical progress and assuming that in corresponding unmet medical needs will be targeted by novel technologies and use of new materials, the pre-market review process should provide for means to make promising devices available to patients in a timely manner. Therefore, the HUD/ HDE concept seems to be a paradigm shift in the patients' best interest in two regards:

Promising devices are allowed to streamline clinical elements and offer patients and their physician's timely access.

FDA was authorized to proactively foster medical innovation policies in distinguishing between healthcare value and financial value inherent to medical devices.

The terms of HUD designations probably lack the criteria of a life threatening condition. The EXCORPed system is a case that illustrates the patient's need for early access to treatment that is life sustaining and improves the quality of life during the waiting time for a second treatment option, the heart transplantation. The regulatory mechanism of designating products into a specific category in order to offer a more flexible premarket assessment route, and therefore may be proposed for implementation in future EU legislation. The regulatory concept of the EU does not offer a centralized structure, which is a prerequisite for harmonized device designations. The delegation of a centralized designation authority is crucial, as well as the nature of mission and tasks accompanied. Since the designation is based on an assessment with regard to fulfillment of a set of predefined criteria, this would be coherent with a proposal of EUCOMED in 2008 [71]. In 2008, EURORDIS suggested creation of the legal category of a "humanitarian medical device" (HMD) [3]. This proposal may impact EU policy on rare diseases in the future and in the advent of the medical device regulations, as reasoned in section 11.2.

Contrasting to the HUD/ HDE concept, an additional criteria should be established in the EU, due to the lessons learned from the U.S. that the unmet medical need should not only be rare but also life threatening or chronically debilitating.

10.1.1 Effectiveness vs. Performance

The non-standard premarket assessment procedure eligible for HUDs exempts the manufacturers from demonstrating reasonable assurance of efficacy and relies primarily on safety and pre-clinical data, on which the rationale for probable benefit is based when weighed. For the approval of a HDE, it is required to demonstrate that "the device is reasonably safe and the probable benefits to health outweigh the risk exposed from its use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment." Consequently, HUDs are exempt from the proof of reasonable assurance effectiveness for market approval [70].

This exemption is for technical reasons directly transferable into the EU legislation, since in the clinical evaluation during conformity assessment the manufacturer has to demonstrate that he conforms to the essential requirements and, based on this proof, his device is reasonably safe and performs as intended. The terms “effectiveness” in U.S. legislation and “performance” in EU legislation are distinct in meaning and impact with regard to their basis to evaluation of clinical outcomes.

Due to the lack of transparency with regard to medical device clinical data, the data requirements of the approximately 70 Notified Bodies in the EU cannot be evaluated to identify a harmonized approval threshold. Despite from the lack of obligation for the NBs to provide public summaries revealing the rationale and grounds for their basis for granting CE mark, a manufacturer’s clinical evaluation remains non-transparent to patients and health-care-providers [57].

10.1.2 Evaluation of Exemption Provision

Generating evidence for the effectiveness of any medical product beyond its clinical development stage is vital for estimating its medical value in terms of clinical outcomes. Postmarket studies of products intended for rare disease populations are crucial for current, complete device information, since for technical reasons, the products’ initial approval often will be based on preliminary data only. Nevertheless, a general exemption from the premarket proof of effectiveness for an “orphan device” should be accompanied by a rigorous life cycle approach. This may not be satisfactory in case of only moderate technical constraints and when generating efficacy data would be feasible, but financially burdensome. If sufficient patient numbers are not available, allowing for enough data to prove reasonable effectiveness, the exemption rule may be applied in order to save costs for the manufacturer during the development stage. Taking into account that, by nature, only significant risk devices will be candidates for the HUD/ HDE procedures, it seems unsatisfactory for ethical and reimbursement reasons to accept a lower level of evidence for healthcare value with rare disease patients. Moreover, considering that the exempted device will be approved for an unlimited amount of time, there is no incentive for the manufacture to capture effectiveness data postmarket. To label the devices as “HUD”, and to allow clinical use only after approval through an institutional review board, does not compensate for the risk of use of a novel device, often implanted, with uncertain degree of benefit, only because the generation of robust data is too costly. Therefore, the

use of such an exemption provision should be eligible only to “orphan devices” that are intended:

1. for diagnosis or treatment of life threatening and debilitating diseases and
2. for use accompanied by mandatory postmarket data collection (clinical and non-clinical).

Due to the absence of alternative treatment options, and taking into account the severity of the condition, preliminary data should be acceptable, if appropriate. Only such circumstances should warrant that patients are exposed to varying levels of protection, which otherwise would be an issue of concern from a public health perspective.

10.2 Orphan Device Policies

With regard to drugs, the US Federal Orphan Drug Act (ODA) of 1983 implemented a pioneering regulatory system. The EU followed in 2004 with the Orphan Drug Regulation. In the U.S., medical devices were not explicitly excluded from the ODA provisions, yet a specific definition and designation for “orphan devices” has not been implemented. By comparison, the EU excluded medical devices from the scope of the regulation that therefore is applicable to drugs only. Although both regulated product groups, drugs and medical devices, share the medical intent, the provisions diverge fundamentally. With regard to evolving novel technologies and medical science progress, novel product features have to be adequately regulated in order to protect the public health.

With regard to “orphan devices designations”, a priority review may be considered for an orphan device clinical trial application.

The basic medical research context should focus more on improved preclinical methodologies, like simulation of specific disease models, generate valuable pre-clinical data as substitutes for lacking clinical data, as it is already under discussion with the FDA’s OOPD [13].

The EU medical device regulatory philosophy, which emphasizes manufacturer’s responsibilities, naturally leads to the industries disinterest in the development of unprofitable products. A regulatory authority, in analogy to the FDA’s OOPD, should be implemented in the EU to stimulate orphan device development. Hence, the pro-

posed concept of an “orphan product designation” recognizes the fact that research and development of new products will not be profitable in terms of cost benefit from industries perspective. The extent and nature of clinical data required for clinical evaluation (Annex X of MDD and AIMD) in the conformity assessment procedure has already dramatically changed with the implementation of the amending Directive of 2007/43/EC in 2010. The newly proposed Medical Device Regulation follows this general course. It puts forth the generation of clinical data for novel high risk devices in clinical trials and the scrutiny of their evaluation. From a scientific and economic perspective, clinical testing for innovative devices is the greatest challenge towards approval and impede final development steps. Besides, the nature and extent of the novelties and complexities of medical devices will increase, (e.g. nanomaterials, software, combination products) adding to market access timelines.

The use of harmonized standards serves as a concretization of the Essential Requirements with regard to the aspects relevant for the technology inherent to a medical device and to the intended use as specified by the manufacturer. The use of harmonized standards is a crucial element of the premarket approval concept in the EU since the manufacturer can utilize them as tools for product design and testing during the pre-clinical development, whereas during the clinical development phase it is theoretically possible to define data requirements for clinical evaluation. The availability of updated, detailed and scientifically sound harmonized standards that establish the nature, extent and scope of required clinical data for Conformity Assessment and CE-mark. Clinical data may be regarded as the strongest impediment to market access, from a manufacturer’s point of view since the clinical phase usually is very time consuming and with enormous financial implications. With respect to orphan devices, the feasibility of deriving clinical effectiveness data may be very limited, in some cases impossible. Hence it often may be necessary to offer more regulatory flexibility for orphan devices in the EU premarket assessment scheme. If available at all, deviation from applicable harmonized standards should be accepted for orphan devices. For this purpose an “orphan device designation” would be the first step to a conformity assessment procedure that is tailored to the specific features of these products.

With the increasing financial risks and costs for life science companies developing medical products, small markets are not attractive due to low return of investment expectations. Of the overall development costs, the translational and in particular the

clinical phase, generating the safety and effectiveness data, are the most expensive steps and most relevant proportion of it and correlate with the rigor applied during premarket evaluation.

Nevertheless, the generation of evidence of effectiveness for any medical product beyond the clinical development phase is vital for the estimation of medical value in terms of clinical outcomes. The phase of postmarket evidence building may be extraordinarily critical for products intended for rare disease populations, since approval can often only be limited to preliminary data for technical reason. I conclude that therefore a general exemption from premarket proof of effectiveness for HUDs should be in any case accompanied by a rigorous life-cycle approach but may not be satisfactory in case of only moderate technical constraints to the evidence building. In case there would be sufficient patients available for data collection in order to demonstrate of reasonable effectiveness, a general exemption is an issue of cost and not of technical constraints. Taking into account that by nature only significant risk devices will be candidates for the HUD/HDE procedures, in seems unsatisfactory for ethical and reimbursement reasons to accept a lower level of healthcare value for the rare disease patients with regard to an orphan device that are legally marketed for an unlimited amount of time. To label the devices as “HUD” one the one hand and to allow clinical use only after approval through an IRB, does not compensate for the risk of use of a significant risk device, often implant, with unknown benefit only because the generation of robust data is too costly. The use therefore should be limited to life-threatening and debilitating diseases alone and be accompanied by mandatory data collection (clinical and non-clinical) of some kind.

The HUD/HDE concept bears elements which seem to be transferrable to the EU regulatory system. The decisive element could be the implementation of a humanitarian use designation. The designation is the result of an assessment with regard to fulfillment of a set of predefined criteria. This was already suggested by EUCOMED [88].

With regard to drugs, a pioneering regulatory system has been implemented in the US three decades ago through the Orphan Drug Act (ODA) of 1983. The EU followed in 2004 with the Orphan Drug Regulation. Whereas in the US medical devices were not explicitly excluded from the ODA provisions, no specific definition and designation for „orphan devices” was implemented. On the contrary, in the EU medical devices

were excluded from the scope of the regulation that explicitly only applies to medicinal product. Although both regulated product groups share the medical intent, the provisions diverged fundamentally with regard to evolving novel technologies and medical science progress leading to novel, more specific product requirements that are to be addressed for public health reason.

The EXCOR medical device is a potentially life-saving, pediatric medical device that has the potential to offer a next-to normal life to a toddler. The benefit of an “orphan device designation”, modeled after the HUD, could be a door-opener in the EU for regulatory and scientific advice, financial incentives like fee waivers, for example. In some EU member state medical device clinical trials need prior approval from a competent authority in addition to IRB approval (Germany, United Kingdom, France, Austria). With regard to “orphan devices designations” some regulatory flexibility could possibly be implemented recognizing low financial revenue expectations.

The concept of orphan product designation recognizes the fact that research and development of new products will not be profitable in terms of cost benefit from industry’s perspective. Already some issues for an „orphan devices designation” can be identified for the EU’s future regulatory system. The extent and nature of clinical data forming the basis of the clinical evaluation (Annex of MDD) in the conformity assessment procedure, has already dramatically changed with the implementation of the amending Directive of 2007/43/EC in 2010. This trend will be vastly followed in the proposed Medical Device Regulation, which probably has to be followed in the near future. It will then be crucial to generate clinical data for novel high risk devices in clinical trials. Therefore, the clinical development will constitute an increasing hurdle from scientific and economic perspective and an impediment to even more “orphanized” devices.

10.3 Combination products

The identification of the primary mode of action, among multiples inherent to the product, may have an impact on the eligibility for designation as an orphan drug. Regarding the trend to combine differently regulated components, a concept for designation medical devices as orphan devices in the EU would be the first step to respond to this trend and to avoid further “orphanization” of combination medical devices intended to treat rare diseases.

10.4 Regulatory Measures to foster Innovation

The development of orphan devices is more probable within a regulatory system allowing for flexibility to some extent, especially with regard to the scope, nature and extent of clinical data required for premarket evaluation. Only adequate scientific and regulatory support may enable small firms, with a lack of experience, to navigate the rather complex regulatory systems. The case of the Wingspan Stent System demonstrates the significance of the labeling and the intended use in narrow populations.

10.5 Pediatric Orphan Devices

The U.S. HDU/ HDE concept demonstrates, that „orphan devices” are an issue, even more essential for pediatric patients, who make up 80% of the entire rare disease population. Regarding pediatric orphan devices, standards and guidance are missing in Europe which would outline a methodology for the development, e.g. through EU guidance. Pediatric aspects have to be taken into account like growth, response of an immature immune system, the small size of physiological structures, etc. The FDA, NIH and associated institutions in the U.S. are currently working on concepts and methodologies (preclinical simulation, Bayesian statistics, etc.) in order to stimulate the development for pediatric medical devices. Due to the absence of alternative treatment options and taking into account the severity of the condition, preliminary data should be acceptable, if appropriate. Exclusively under such special circumstances it may be acceptable that patients are exposed to varying levels of protection, which otherwise would be an issue of concern from a public health perspective.

11 Conclusions and Outlook

11.1 Transparency and Involvement of Patients

Both medical device legislations share common elements like risk classification, pre-market assessment and postmarket vigilance and the regulatory elements risk management, application of a quality systems, design dossier and labeling. Nevertheless, the administrative structures are contrasting regarding the centralization of authorities at the U.S.'s FDA versus the decentralized and supranational system in the EU. With regard to HUDs and orphan devices, the U.S.'s context may have accelerated the political process behind the regulatory concept intended for fostering therapeutic innovation for small populations. The FDA is closely tracked by the public and transparency policies have a high priority. The patient's interests therefore counterbalance

the interests of the medical industry. This interdependency results in regulatory processes taking into account all stakeholders' perspective, in particular the patient's. With regard to EU patient advocacy, the FDA's long-term experience with humanitarian use devices is paramount due to the awareness raising effect. The discussion in the U.S. is currently focusing on pediatric humanitarian use devices and is based on the assumption of various medical needs. In a next step of the process of fostering medical device innovation, those needs will be identified and systematically assessed by the U.S.'s agencies.

11.2 Proposal of Designation for Orphan Medical Devices in the EU

The U.S. concept seems to be well suited as a model for the HDE designation procedure for the EU. The implementation of an "orphan device designation" procedure into revised EU legislation is therefore proposed. As argued in section 11, the beneficial impact of the proposed procedure on regulatory flexibility options may not be underestimated. Concurrently to the implementation of medical device regulations in the EU, the extend of harmonization of third-party reviews may improve and, through the enactment of possible implementation measures of the European Commission, further determine details of the conformity assessment procedures.

11.3 International Collaboration

According to Steven Groft, the Director of the Office of Orphan disease research states in a FDA workshop in 2014 [13], that he is of the opinion, that "the key to all of this is really developing the partnerships and the collaborations with the patient organizations, the academic researchers, the biopharmaceutical medical devices industry." He states that "It is key to everything we have been doing with orphan drugs and rare diseases since the 1980s and I think it still holds true today that success is gained when you do establish these partnerships and these collaborations." [13]. Any effort concerning diseases and conditions that are rare and pediatric are probably more effective in international collaboration, which is therefore proposed regarding the further development of guidelines and standards for device development in special populations.

12 References

1. European Rare Diseases Organisation (2008) Contribution to the Public Consultation “Recast of Medical Devices Directives”. Retrieved from:
http://www.eurordis.org/IMG/pdf/EURORDIS_Statement_on_MDs_-_FINAL_-_July_2008.pdf (11.02.15)
2. Safe Medical Devices Act of 1990 P. L. 101-629, 104 Stat. 4524-4525 Section 14 Humanitarian Device Exemption, subsections a-c, amending subsection (m) of section 520 of the FD&C Act
3. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning biocidal products on the market, 2007, O. J. L 247/21
4. Sachverständigenrat Gesundheitswesen. (2014). Gutachten: Bedarfsgerechte Versorgung: Perspektive für ländliche Regionen und ausgewählte Leistungsbereiche. Kapitel 3: Versorgung mit Medizinprodukten, pp. 141-254. Verlag Hans Huber, Hogrefe AG, Bern
5. Food and Drug Administration (2014) Code of Federal Regulations, Title 21 Volume 8 Part 814.3 Definitions, sections (m) HDE and (n) HUD. Retrieved from:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=814.3> (11.02.2015)
6. Mason S in: The Textbook of Pharmaceutical Medicine. Griffin JP, Posner, J, Barker, GR (eds.). (2013) 7th Edition. Part II Regulation, Chapter 21 European Regulation of Medical Devices, pp. 418-434. John Wiley & Sons Ltd, Publication, Belfast
7. Food and Drug Administration (2014) Draft Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation). Retrieved from:

<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm273902.htm> (11.02.2015)

8. Regulation (EC) No 141/2000 on orphan medicinal products, 2000, O. J. L 18/1
9. Food and Drug Administration (2014) Device Advice: Comprehensive Regulatory Assistance: Investigational Device Exemption (IDE) retrieved from:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm046164.htm> (11.02.2015)
10. Food and Drug Administration (2015) FDA Safety Communication: Narrowed Indications for Use for the Stryker Wingspan Stent System. Retrieved from:
<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm> (11.02.2015)
11. Groft S, De la Paz MP in: De la Paz MP, Groft SC (eds.) (2010). Rare Diseases Epidemiology. Advances in Experimental Medicine and Biology. Part I Rare Diseases- Avoiding Misperceptions and Establishing Realities: The Need for Reliable Epidemiological Data, pp. 3-16, Springer, Dordrecht
12. Food and Drug Administration Center for Devices and Radiological Health (2014): Complex Issues in Developing Medical Devices For Pediatric Patients Affected By Rare Diseases. Retrieved from:
<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm367656.htm> (11.02.2015)
13. Institute of Medicine Committee on Accelerating Rare Diseases Research and Orphan Product Development, Field MJ, Boat TF (2010) Rare Diseases and Orphan Products: Accelerating Research and Development. National Academies Press, Washington (DC).
14. International Rare Diseases Research Consortium. Homepage retrieved from: <http://www.irdirc.org/> (19.01.2015)

15. Rat der Europäischen Gemeinschaft (1985) Entschliessung des Rates über eine neue Konzeption auf dem Gebiet der technischen Harmonisierung und der Normung (85/C 136/01). Abl Nr. C 136/1.
16. European Commission. (2014). Europe's challenges COM(2008) 679 final and Council Recommendation of 8 June 2009 on an action in the field of rare diseases 2009/C 151/02. Retrieved from:
http://ec.europa.eu/health/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf (11.02.2015)
17. Samuels-Reid JH, Blake ED (2014) Pediatric medical devices: a look at significant US legislation to address unmet needs. Expert Review of Medical Devices 11:169–174
18. Food and Drug Administration. (2014). Draft Guidance for Industry and Food and Drug Administration Staff: De Novo Classification Process (Evaluation of Automatic Class III Designation). Retrieved from:
<http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm273902.htm> (11.02.2015)
19. Regulation (EU) No 1025/2012 on European Standardisation and amending Council Directives 89/686/EEC and 93/15/EEC and Directives 94/9/EC, 94/25/EC, 95/16/EC, 97/23/EC, 98/34/EC, 2004/22/EC, 2007/23/EC, 2009/105/EC and 2009/23/EC of the European Parliament and of the Council, 2012, O. J. L 316
20. Food and Drug Administration (2014) Code of Federal Regulation, Title 21 Part 860.7 sections (c)(2), (d)(1) retrieved from:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=860.7> (11.02.2015)
21. Deutsches Institut für Normung. Homepage retrieved from:
<http://www.din.de/cmd?level=tpl-home&contextid=din> (11.02. 2015)
22. De Marco CT (2011) Medical Device Design and Regulation. American Society of Quality, Quality Press, Milwaukee, Chapter 2 Medical Device Design, Part 3 Design Inputs and Outputs, pp. 61-65

23. European Commission (2008) Communication on Rare Diseases: Europe's challenges. COM(2008) 679 final. Retrieved from:
http://ec.europa.eu/health/ph_threats/non_com/docs/rare_com_en.pdf.
(11.02.2015)
24. Council of the European Union (2009) Recommendation on an action in the field of rare diseases (2009/C 151/02), O. J. C 151/7
25. European Commission (2014) Implementation report (COM(2014) 548 final) on the Commission Communication on Rare Diseases: Europe's challenges [COM(2008) 679 final] and Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02). Retrieved from:
<http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM:2014:548:FIN>
(11.02.2015)
26. European Commission (2010) Guidelines on Clinical Investigation: A Guide for Manufacturers and Notified Bodies. MEDDEV 2.7/4. Retrieved from:
http://ec.europa.eu/growth/sectors/medical-devices/dialogue-parties/working-groups/cie_wg_index_en.htm. (11.02. 2015)
27. Orphan Drug Act of 1983 P. L. 97-414, 96 Stat. 2049
28. De Marco CT (2011) Medical Device Design and Regulation. American Society of Quality, Quality Press, Milwaukee, Chapter 1 Background and Regulatory Environment, pp. 1-51
29. European Commission (no date) Guidance MEDDEVs. Homepage of the European Commission. Retrieved from:
http://ec.europa.eu/growth/sectors/medicaldevices/documents/guidelines/index_en.htm (11.01.2015)
30. Rare Disease Act of 2002 P. L. 107-280, 116. Stat. 1988
31. Fraser AG, Daubert J-C, Van de Werf F, Estes NAM, Smith SC, Krucoff MW, Vardas PE, Komajda M, participants (2011) Clinical evaluation of cardiovascular devices: principles, problems, and proposals for European regulatory reform. Report of a policy conference of the European Society of Cardiology. European Heart Journal 32:1673–1686

32. Pediatric Research Initiative. 42 USC §284h, P. L. 106-310, P. L. 190-482, P. L. 110-154
33. Food and Drug Administration (1996) Final Rule to Implement the Provisions of the Safe Medical Devices Act of 1990 regarding Humanitarian Use Devices. Federal Register Vol. 61, No. 124, Rules and Regulations. pp. 33232-33248
34. Food and Drug Administration (2014) Center of Devices and Radiological Health. Humanitarian Device Exemption. Overview. Retrieved from: <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/HumanitarianDeviceExemption/> (11.02.2015)
35. Federal Food Drug and Cosmetic Act of 1938 P. L. 75-717, 52 Stat. 1040 (1938)
36. Food and Drug Administration. Center of Medical Devices and Radiological Health (2014) Draft Guidance for Industry and FDA Staff: Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions. Retrieved from: <http://www.fda.gov/RegulatoryInformation/Guidances/ucm393879.htm> (11.02.2015)
37. Food and Drug Administration. Center of Medical Devices and Radiological Health. (2014) Draft Guidance for Industry and FDA Staff: Balancing Pre-market and Postmarket Data Collection for Devices Subject to Premarket Approval. Retrieved from: <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm393882.htm> (11.02.2015)
38. Phillips MI (2013) Big Pharma's new model in orphan drugs and rare diseases. Expert Opinion on Orphan Drugs 1:1–3
39. Federal Food Drug and Cosmetic Act 21 U.S.C. §§ 301-366f. P. L. 75-717, Stat. 1040 (1938)

40. European Commission. DG Health and Food Safety (no date) Medical Devices: Regulatory Framework. Retrieved from:
http://ec.europa.eu/growth/sectors/medical-devices/regulatory-framework/index_en.htm. (11.02.2015)
41. Food and Drug Administration Amendments Act of 2007 (P. L. 110-85)
42. World Health Organisation (2014) Second WHO Global Forum on Medical Devices. Priority Medical Devices for Universal Health Coverage. P. 37, WHO Press, Geneva
43. Eccelston, RC. Hernández, A (ed.). World Health Organisation (2001). A Model Regulatory Program for Medical Devices. Pan American Health Organization, Washington, DC. Section II, pp. 9-34.
44. Food and Drug Administration (2015) Standards: Medical Devices. Retrieved from:
<http://www.fda.gov/medicaldevices/deviceregulationandguidance/standards/default.htm> (11.02.2015)
45. 21 USC §353 Exemptions and consideration for certain drugs, devices, and biological products section (g) Regulation of combination products, United States Code, 2006 Edition, Supplement 5, Title 21-Food and Drugs, p. 152
46. Food and Drug Administration (2014) Draft Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff: Humanitarian Device Exemption (HDE): Questions and Answers. Retrieved from:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm389154.htm> (11.02.2015)
47. Food and Drug Administration (2013) Guidance for Industry and FDA Staff: Humanitarian Use Device (HUD) Designations Retrieved from:
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM336515.pdf>. (11.02.2015)
48. De Joncheere, K. World Health Organization. International Medical Device Regulatory Forum (2013) Regulatory convergence. WHO's perspective. Re-

rieved from: <http://www.imdrf.org/docs/imdrf/final/meetings/imdrf-meet-130319-france-presentation-who-perspective.pdf> (11.02.2015)

49. Federal Food, Drug and Cosmetic Act of 1938 P. L. 75-717, 52 Stat. 1040,-1041 codified at 21 USC Chapter 9 §§ 301 et seq.
50. Medical Device Amendments of 1976 P. L. 94-295, 90 Stat. 539-583 Section 515 Premarket Approval
51. Food and Drug Administration. Center of Medical Devices and Radiological Health (2011) Draft Guidance for Industry and FDA Staff: Classification of Products as Drugs and Devices & Additional Product Classification Issues. Retrieved from:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm258946.htm>
(11.02.2015)
52. Medtronic (no date) About Medtronic Deep Brain Stimulation for Movement Disorders. Retrieved from: <http://professional.medtronic.com/pt/neuro/dbs-md/edu/about/index.htm#.VPWEV3ZV8q9> (11.02.2015)
53. European Commission. (2009). Guidelines on Medical Devices Clinical Evaluation: A Guide for Manufacturers and Notified Bodies. MEDDEV 2.7.1 rev 3. Retrieved from: http://ec.europa.eu/growth/sectors/medical-devices/documents/guidelines/index_en.htm (11.02.2015)
54. Miocinovic S, Somayajula S, Chitnis S, Vitek JL (2013) History, applications, and mechanisms of deep brain stimulation. JAMA Neurol 70:163–171
55. Food and Drug Administration (2012) Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval. Retrieved from:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm267829.htm>
(11.02.2015)
56. Food and Drug Administration. (2012) Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval. Retrieved from:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm267829.htm>

(11.02.2015)

57. Sorenson C, Drummond M (2014) Improving Medical Device Regulation: The United States and Europe in Perspective. *The Milbank Quarterly* 1–37
58. Food and Drug Administration (2014). Draft Guidance for Industry and FDA Staff: Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval. Retrieved from:
<http://www.fda.gov/RegulatoryInformation/Guidances/ucm393882.htm>
(11.02.2015)
59. Food and Drug Administration (2014) Code of Federal Regulations, Title 21, Volume 8 Part 860.7 Medical Device Classification Procedures. Retrieved from:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?R=860.7> (11.02.2015)
60. Becker K in: Becker KM, Whyte JJ (2006) *Clinical Evaluation of Medical Devices*. Humana Press, Totowa, New Jersey. Chapter 1, pp. 3-20
61. Kaplan AV, Baim DS, Smith JJ, Feigal DA (2004) Medical Device Development. *Circulation* 109:3068–3072
62. Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, 1990, O. J. L 189
63. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, O. J. L 169
64. Directive 98/79/EC of the European Parliament and of the Council of October 1998 on in vitro diagnostic medical devices, 1998, O. J. L 331
65. Institute of Medicine. Field MJ, Field MJ, Tilson H (eds.) (2006). *Safe Medical Devices for Children*. National Academies Press, Washington, DC
66. Ulrich LC, Joseph FD, Lewis DY, Koenig RL (2013) FDA's Pediatric Device Consortia: National Program Fosters Pediatric Medical Device Development. *Pediatrics* 131:981–985

67. Kramer DB, Shuai X, Kesselheim AS (2012) Health Law, Ethics, and Human Rights. *New England Journal of Medicine* 1–8
68. Food and Drug Administration (2002) Device Advice: Comprehensive Regulatory Assistance: Premarket Approval Submissions: Premarket Approval (PMA) retrieved from:
<http://www.fda.gov/Medicaldevices/Deviceregulationandguidance/Howtomarketyourdevice/Premarketsubmissions/Premarketapprovalpma/Default.Htm>.
(11.02.2015)
69. Food and Drug Administration (2013) Code of Federal Regulation Title 21 Volume Part 814 subpart H retrieved from:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814> (11.02.2015)
70. Food and Drug Administration (2012) Executive Summary prepared for the meeting of the Neurologic Device Panel: Current Knowledge of the Safety and Effectiveness of the Wingspan Stent System with Gateway PTA Balloon Catheter for the Treatment of Intracranial Arterial Stenosis. Retrieved from:
<http://www.fda.gov/advisorycommittees/calendar/ucm291568.htm>
(11.02.2015)
71. EUCOMED (2008) Eucomed Contribution to the Public Consultation on Rare Diseases: Europe's Challenges. Retrieved from:
<http://www.eucomed.org/library/public-consultations>
(11.02.2015)
72. Food and Drug Administration. Office of Orphan Products Development. Lewis D (2010) Humanitarian Use Devices (HUDs) Humanitarian & Humanitarian Device Exemptions (HDEs). Retrieved from:
<http://www.iom.edu/~media/Files/Activity%20Files/Research/OrphanProductResearch/10-FEB-04/LewisHUD.pdf>
(11.12.2014)
73. Food and Drug Administration. (2010) Guidance for HDE Holders, Institutional Review Boards, Clinical Investigators, and Food and Drug Administration Staff- Humanitarian Device Exemption (HDE) Regulation: Questions and An-

swers. Retrieved from:

<http://www.fda.gov/RegulatoryInformation/Guidances/ucm110194.htm>

(11.02.2015)

74. Fins JJ, Mayberg HS, Nuttin B, Kubu CS, Galert T, Sturm V, Stoppenbrink K, Merkel R, Schlaepfer TE (2011) Misuse Of The FDA's Humanitarian Device Exemption In Deep Brain Stimulation For Obsessive-Compulsive Disorder. *Health Affairs* 30:302–311
75. Bernad DM (2009) Humanitarian Use Device and Humanitarian Device Exemption regulatory programs: pros and cons. *Expert Review of Medical Devices* 6:137–145
76. Food and Drug Administration. Center for Medical Devices and Radiological Health. (2014) Public Workshop – Complex Issues in Developing Medical Devices for Pediatric Patients Affected by Rare Diseases. Transcript retrieved from:
<http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm367656.htm>
(11.02.2015)
77. Institute of Medicine. Committee on Accelerating Rare Diseases Research and Orphan Product Development. Field MJ, Boat TF (eds.) (2010) *Rare Diseases and Orphan Products: Accelerating Research and Development*. National Academies Press (US), Washington (DC). Summary; Recommendation 7-4, pp. 1-14
78. Alpert S in: Institute of Medicine. Hanna KE, Manning FJ, Bouxsein P, Pope A (eds.) (2001) *Innovation and Invention in Medical Devices: Workshop Summary*. Chapter 4, p. 50-51. National Academies Press, Washington, DC.
79. Food and Drug Administration. Center for Devices and Radiological Health. (2014). *HDE Approvals: Listing of CDRH Humanitarian Device Exemptions*. Retrieved from:
<http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm> (11.02.2015)

80. Food and Drug Administration. Center for Devices and Radiological Health. Communications: Narrowed Indications for Use for the Stryker Wingspan Stent System: FDA Safety Communication. Retrieved from:
<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm314600.htm>
(11.02.2015)
81. Samaniego EA, Tari-Capone F, Linfante I, Silva CF, Spilberg G, Gounis M, Wakhloo AK, Dabus G (2013) Wingspan experience in the treatment of symptomatic intracranial atherosclerotic disease after antithrombotic failure. Journal of Neurointerventional Surgery 5:302–305
82. Berlin Heart EXCOR® Pediatric Ventricular Assist Device (VAD) - H100004. Retrieved from:
<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cftopic/pma/pma.cfm?num=H100004> (11.02.2015)
83. Mayberg HS, Fins JJ, Nuttin B, Kubu CS, Sturm V, Stoppenbrink K, Merkel R, Schlaepfer TE (2011) Misuse Of The FDA’s Humanitarian Device Exemption In Deep Brain Stimulation For Obsessive- Compulsive Disorder. Health Affairs 1–11

Erklärung

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

Wachtberg, den 11.02.2015