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Title: Overview of the Regulation of Medical Devices and Drugs* in the United States of America, and the European Union.

*For the purposes of this document, the term “Drug” is used when referring to “Medicinal Product” in the EU, and “Prescription Drugs” in the US.

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Abstract

This article provides an overview of the regulation of medical devices and drugs in the European Union and United States. It is important for all stakeholders involved in bringing a medical device or drugs to market to have an understanding of the regulatory requirements involved in this process. This article demonstrates that the regulation of these products is an extremely complex process.

Key Words: Medical Device Regulation, Drug Regulation, EU and US Regulatory Frameworks, Regulatory Agencies

Introduction

The medical device and drug regulatory frameworks are extremely complex, which can significantly delay manufacturers attempting to bring new devices and drugs to the international market. Such delays can result in patients not receiving timely benefits from technological breakthroughs. An understanding of these regulations is critical for all such stakeholders in order to avoid or minimise these delays.

Regulation of Medical Devices in the EU

The regulation of medical devices in the European Union (EU) is relevantly recent in comparison to the United States (US). The regulation of medical devices in the EU began in the mid 1990s whereas it began in the U.S. in the mid 1930s. In the EU prior to the mid 1990s each country before this had its own legislation and subsequently the approval process was different in each country. Today medical devices in the EU are regulated by three Directives:

1. The European Council Directive 93/42/EEC¹. This is known as the Medical Devices Directive. This Directive covers the majority of medical devices, from simple non-sterile drainage containers to complex devices such as interventional cardiology catheters.
2. The European Council Directives 90/385/EEC². This is known as the Active Implantable Medical Devices Directive (AIMD Directive). This directive is concerned with powered implantable devices such as pacemakers.

3. The European Council Directive 98/79/EC³. This is known as the In Vitro Diagnostic Directive (IVD Directive).

The European Community's definition for medical devices can be found in the Medical Device Directive 93/42/EEC¹. Medical devices are defined in the EU as;

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

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of physiological process;
- control of conception; and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means”

Medical devices vary greatly in complexity and application. They can range from simple bandages and medical thermometers to advanced devices such as magnetic resonance imaging machines (MRI) and x-ray machines. The classes of devices are; Class I, Class IIa, Class IIb and Class III. The classes are based upon contact time, invasiveness and active or not. The classification system is a risk based system based on the vulnerability of the human body taking account of the potential risks associated with the devices. This system allows the use of a set of criteria that can be

combined in various ways in order to determine classification of a variety of medical devices. In such a system the level of control relates to the level of potential hazard inherent in the type of device concerned. Table 1 shows the different classifications, the corresponding risk levels and examples of devices in each class.

Insert Table 1 here

In contrast to the US regulatory system, where there is one principle regulatory body; the Food and Drug Administration (FDA) that oversees the medical device system in a centralised manner, in the EU there is a multifaceted system with roles for a number of authorities including private entities. There are 5 authorities involved with the regulation of medical devices in the EU:

1. The European Commission
2. The Competent Authorities
3. The Notified Bodies
4. The European Union Authorization Representatives
5. Manufacturers

1. **The European Commission:** The European Commission is the EU's executive body and is responsible for proposing legislation and implementing decisions and for the general day-to-day running of the Union. The department responsible for medical devices and drugs is the Directorate-General for Health and Consumer Protection.

2. **Competent Authorities:** A competent authority is a body with authority to act on behalf of the government of the Member State to ensure that the requirements of the medical device directives are transposed into National Law and are applied. The government of each Member State is required to appoint a Competent Authority responsible for medical devices. The Competent Authority reports to the Minister of Health in the Member State. Responsibilities of the competent authorities include appointing Notified Bodies, overseeing the work of the Notified Bodies, surveillance of medical devices on sale in their own Member State and the assessment of adverse incidents.

3. **Notified Bodies:** Notified Bodies are certification organisations. Their role is in assessing manufacturers' compliance with the requirements of European medical device law, signifying compliance by granting certificates and monitoring it through regular audits. The scope of a Notified Body's role depends on the class of the product. In the case of a Class III device, for instance, a Notified Body will examine the product design and audit the quality system. A Notified Body will not get involved in a Class I device unless it is sold sterile and/or has a measuring function, and then its scrutiny is limited to those aspects. Notified Bodies are privately-held for-profit organizations. Competent Authorities of member states subcontract Notified Bodies which perform the certification of goods on the member state's behalf. In other words, in contrast with the US approach, manufacturers are not obliged to undergo governmental review in order to get access to the market in Europe.

The European Commission, Competent Authority and Notified Bodies when combined together are more or less comparable to the function of the FDA. The

notified body is roughly equivalent to the FDA's inspection branch. Notified bodies, however, do not have any enforcement powers that the inspection branch has.

4. Authorised Representative: An "authorised representative means any natural or legal person established in the Community who, explicitly designated by the manufacturer, acts and may be addressed by authorities and bodies in the Community instead of the manufacturer with regard to the latter's obligations under this Directive" 4. An Authorised Representative cannot fully assume the regulatory responsibilities of the manufacturer because that would imply it has powers of inspection and coercion that the manufacturer would never tolerate. The Authorised Representative must have sufficient regulatory expertise to be able to act on behalf of the manufacturer in compliance matters when so requested. As the law stands today, there are no restrictions as to who can be an Authorised Representative. No authorisation is needed and no qualifications are required.

5. Manufacturer: A manufacturer or the person placing the product on the market is defined as "the natural or legal person with responsibility for the design, manufacturer, packaging and labelling of a device before it is placed on the market under his own name, regardless of whether these operations are carried out by that person himself or on his behalf by a third party"¹. This definition permits all actual manufacturing operations to be delegated to a third party as long as the "legal manufacturer" retains responsibility and places the products on the market under its own name. This implies that distribution companies that sell third-party manufactured products under their own name may very well be considered legal manufacturers. It is important to understand that despite the possibility of being able

to delegate virtually all manufacturing tasks, the legal manufacturer is ultimately responsible for any noncompliance, even if it rises from the actions or failings of a subcontractor.

Medical Device Pathway to Market in EU

In order to commercialise medical devices in the EU, manufacturers must obtain CE marking certification and affix the CE marking as part of their device registration efforts. CE is an abbreviation of French "Conformite Europeenne" meaning "European Conformity". This mark is not a guarantee of safety. It signifies that the manufacturer claims that the relevant *Essential Requirements* in the Directives are complied and the device is fit for its intended purpose. It also signifies that the product can be freely marketed anywhere in E.U. without further control.

The *Essential Requirements* in the Medical Device Directive 93/42/EEC can be divided in two groups: the first refers to a set of general requirements for safety and performance that applies to all devices. The second is a list of specific and technical requirements regarding design and manufacturing that may or may not apply depending on the nature of the device. Manufacturers have to demonstrate and document compliance with the regulations and issue a declaration of conformity. In certain situations, such as class I sterile devices, it may be require the involvement of a Notified Body. Class III devices require clinical studies, barring when data already exists.

In the case of devices for clinical investigation and those that are custom made, the CE mark is not mandatory. The manufacturer has to follow Annex VIII of the

Medical Device Directive regarding the Statement Concerning Devices for Special Purposes¹ and declare that their products conform to the *Essential Requirements*. Clinical data is intended to demonstrate the device's safety and that it performs as intended by the manufacturer. In this context, the expression has a broad meaning and includes everything from bench testing to clinical trials in humans. It can be compiled from the literature or result from specifically designed clinical investigations. If the later path is chosen, manufacturers must abide the standard ISO 14155⁵ and the clinical trials must be pre-approved by a Competent Authority.

Regulation of Medical Devices in the US

Regulation of medical devices in the US began in 1938 and reflected the technologically relatively simple devices then on the market. In 1938, the Federal Food, Drug, and Cosmetic Act was passed, the Act gave FDA multiple responsibilities and authorities for drugs and medical devices, including designating adulterated or misbranded products as in violation of the law, as well as the authority to seize adulterated or misbranded medical devices. Shortcomings of the drug and device regulatory structure were becoming evident as more drugs and devices came on the market. There was an increasing need for premarket review of devices rather than just enforcement by seizure of problematic devices. The first step to address these problems came with the passage of the Drug Amendments of 1962 legislation. It was also becoming clear that devices should be treated differently from drugs and that no single form of regulation would be appropriate for all medical devices. The resultant 1976 Medical Device Amendment mandated testing and FDA approval of medical

devices. Most of the regulations for Medical Devices can be found in Title 21 Code of Federal Regulations Part 800 to Part 1299⁶ and are enforced by the FDA.

The US's definition for medical devices can be found in the Title 21 Code of Federal Regulations (21 CFR) of the Federal Food, Drug and Cosmetics Act (FDC Act)⁷. In the Act devices are defined as;

“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 that does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and that is not dependent upon being metabolized for the achievement of any of its primary intended purposes”

The Medical Device Amendment gave rise to three classes of medical devices. Each class required a distinct regulation level for safety and effectiveness. In the US the classification system for medical devices is based on the level of risk to the patient,

the intended use; and the indication for use. There are three classes of devices; Class I, II, and III. Medical devices are classified into three categories (regulatory control increases from Class I to Class III): Class I devices are defined as non-life sustaining. These products are the least complicated and their failure poses little risk. Class II devices are more complicated and present more risk than Class I, though are non-life sustaining. These may be subject to specific performance standards. Class III devices sustain or support life, so that their failure is life threatening. These products are subject to specific performance standards. Table 2 shows the different classifications, the corresponding risk levels and examples of devices in each class

Insert Table 2 here

Class I is the lowest level device with the least amount of regulatory control due to the low level of risk to the patient. These devices are subject to *General Controls* which includes *Establishment Registration* by the manufacturers, distributors, repackages and relabellers; listing in the FDA database; Good Manufacturing Practices ; labelling of the medical device; and a 510(k) Premarket Notification. The majority of Class I devices are exempt from premarket notification and Good Manufacturing Practices.

Class II medical devices have more risk than a Class I device and require a higher level of regulatory control. In addition to *General Controls* they are also subject to *Special Controls*. *Special Controls* include additional labelling requirements,

mandatory performance standards, and post-market surveillance. Some Class II devices are exempt from premarket notification; however, they are subject to limitations if they present a new intended use or questions new issues of safety and effectiveness.

Class III medical devices represent the highest risk level of the classifications and require the most rigorous review and regulatory oversight. The majority of class III devices require FDA approval of a *premarket approval application* (PMA). Approval of the PMA normally requires clinical data demonstrating reasonable assurance that the device is safe and effective in the target population. Class III medical devices are used to support or sustain life, prevent impairment, or present a potential for increased risk of illnesses or injury to the user. In addition to the level of risk, other devices may be included in the Class III category such as: if the device is found to be not *substantially equivalent* (did not meet the requirement for a 510(k)), or does not have a *predicate* (a device that has been cleared through a 510(k) review) to compare to for pre-market review. A 510(k) submission is a premarket notification submitted to the FDA to demonstrate that the medical device to be marketed is as safe and effective or substantially equivalent to a legally marketed device. Devices that meet the requirements for the 510(k) are given the designation of “*cleared*”, devices that undergo a Class III review and meet the requirements are given the designation of “*approved*”.

The FDA regulate the majority of medical devices in the Center for Device and Radiological Health (CDRH) whose main responsibility is to regulate manufacturers, repackages, re-labellers, developers of investigational medical devices and importers of medical devices ⁸. The FDA carries out its medical device responsibilities by;

assessing new products before they are marketed for conformance to requisite design, engineering bench tests, and data from animal trials or clinical trials in patients; assuring quality systems are in place in the device manufacturing plants through inspection and enforcement activities. They also collect and monitor adverse effects from marketed products and investigations, and take actions to prevent injury or death.

Medical Device Pathway to Market in the US

In order to market a medical device, there are four options: ‘*exempt*’, *510(k)*, *premarket approval* (PMA) and the *humanitarian device exemption* (HDE). Clinical studies of investigational devices must comply with FDA’s investigational device exemption regulations.

Most class I and some class II devices are exempt from the premarket notification 510(k) requirements. They still, however, have to comply with the *General Controls*. They must be manufactured under a quality assurance program, be suitable for the intended use, be adequately packaged and properly labelled, and have establishment registration and device listing forms on file with the FDA.

The 510(k) process is a 90-day review procedure based on the view that the device to be marketed is at least as safe and effective, that is, *substantially equivalent* (SE) - predicate device -to one that was already approved by the FDA and is not subject to PMA. Most class II devices follow this path. In addition to the premarket notification 510(k) and the *General Controls*, devices must comply with special controls, namely

performance standards, guidance documents or implementation of post-market surveillance.

PMA can be equated to the design dossier that is necessary to market European class III devices. It is the most comprehensive type of device marketing application. It is the process to evaluate the safety and effectiveness of class III medical devices. Although, FDA regulations provide 180 days to review the PMA and make a determination, the process can take between 6 months to 2 years. This depends on factors such as the report of clinical studies, quality of documents and the amount of time necessary for the manufacturers to response to FDA concerns.

Previous to the FDA Modernization Act of 1997 ⁹, if an innovative device was found *not substantially equivalent* (NSE), it was classified as class III and a PMA was required resulting in a conflict between the need of being innovative and a more complex commercialization process. Currently, the *De Novo* process allows the reclassification of the devices to class I or class II providing a simpler route to market for novel low risk devices. This process, which has to begin within 30 days of an NSE letter, has a review period of 60 days and, if the device is classified into class I or II, the applicant is given an approval order to market the device. However, if it is decided that the device must remain in the class III category, it cannot be marketed until the applicant has obtained an approved PMA.

The use of the *De Novo* route is a strategic decision and depends upon the product. The choice of such route is influenced by factors such as the device's market and other barriers to market entry. For example, if there is insignificant patent protection, manufacturers can benefit from a class III classification because it will

represent to competitors a barrier to market entrance. *The Humanitarian Device Exemption* (HDE) is a specific path for class III medical devices designed to address diseases and conditions that affect fewer than 4000 patients in the United States per year. This path aims to be an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting small populations.

An investigational device is a medical device which is the subject of a human research study to evaluate its safety and/or effectiveness. A company developing an investigational medical device in the US can only conduct clinical studies of the device in the US if they obtain an *Investigational Device Exemption* (IDE) from FDA.

Regulation of Drugs in the EU

A drug may be placed on the EU market only when a *marketing authorisation* has been issued by the regulatory authority of a Member State for its own territory or when an authorization is granted for the entire Community. Drugs can be marketed in the EU only when data supporting their quality, safety and efficacy have been assessed and marketing authorisation granted.

Article 1 (2) of European Council Directive 65/65/EEC defines a drug as follows¹⁰:

“Any substance or combination of substances presented for treating or preventing disease in human beings or animals.

Any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings or in animals is likewise considered a drug”

In the EU drugs are covered by the internal market principal of the free movement of goods. Throughout much of the 20th century, in the absence of a harmonised EU legislative framework, individual Member States enacted national legislation that regulated drugs for human use. With the adoption of Council Directive 65/65/EEC of 26 January 1965, this stipulated that a drug may only be placed on the market in the E.U after a *marketing authorisation* has been granted. Since 1965, the EU pharmaceutical legislation framework has been extended and developed with the aim of protecting public health and preserving the free movement of drugs.

In 1995, a new system for authorising drugs entered into law. It was based upon two separate Community procedures for granting a *marketing authorisation* for a drug: the Centralised Procedure and the Mutual Recognition procedure. The Centralised Procedure was administered through European Medicines Agency (EMA) and Member State Competent Authorities were responsible for the Mutual Recognition procedure. In addition, a purely national authorisation was possible for a product that was marketed in only one Member State.

The new pharmaceutical regulations (Directive 2004/27/EC¹¹) that came into force in 2005 provided another option to authorise drugs within the EU: the Decentralised Procedure. The principal purpose of medical product regulation in the EU is to safeguard public health. This purpose is complicated by the fact that the EU is not a single nation but consists of multiple, independent countries, each with its own legislative framework and cultural, medical and political practices. As part of the European Community, each Member State is subject to relevant EU law.

In the E.U. there a number of institutional players that are involved with the regulation of drugs. The EMA is responsible for the scientific evaluation of medicines and consequently plays a pivotal role in the approval of pharmaceutical products in the E.U. The EMA is an analogue to the FDA. The EMA is not a law enforcement agency. EMA is responsible for overseeing drugs authorised for use within the Community and maintaining relevant databases. The agency also coordinates pharmacovigilance. There is no corresponding institution for medical devices in the EU.

The European Commission is the EU civil service. The pharmaceutical sector currently is in the Directorate-General Health and Consumers. The European Commission also chairs both the Pharmaceutical and Standing Committees. The former is the pharmaceutical sector's policy making unit; the latter is the Commission's decision-making arm for refusing or granting authorisation.

The Route to Market for EU Drugs

Regardless of the registration procedure employed, the *marketing authorisation* is granted to a single party referred to as *the Marketing Authorisation Holder* (MAH). The MAH must be established within the European Economic Area. The marketing authorisation permits the MAH to market the product in the applicable region and, in so doing, places a number of obligations upon the MAH. These include maintaining the marketing authorisation to reflect technical and scientific progress, releasing the product onto the market in accordance with EU law (through a Qualified Person) and providing pharmacovigilance and scientific information.

Three marketing authorization routes are available in Europe (for products authorised in more than one Member States); the Mutual Recognition Procedure, the Decentralised Procedure and the Centralised Procedure. In the Mutual Recognition Procedure, which is applicable to the majority of conventional drugs, after the data has been evaluated by the relevant member state regulatory agency, the initial marketing authorisation is recognised by other Member States. The Mutual Recognition Procedure, therefore, can result in multiple, identical marketing authorisations. The current legislation allows the Mutual Recognition Procedure only for products that already have a marketing authorisation. In the Decentralised Procedure, this is also applicable to the majority of conventional drugs. The evaluation is also performed by one national regulatory agency, but the *marketing authorisation* is usually granted in other Member States only after all Member States involved reach agreement.

The Centralised Procedure, which is mandatory for human medicines derived from biotechnological processes, for treatment of rare disorders (orphan drugs) and for drugs for human use which contain an active substance authorised in the Community after 20 May 2004 and which are for the treatment of cancer, AIDS, diabetes or neurodegenerative disorders. In the Centralised Procedure, the Committee for Drugs for Human Use (CHMP) evaluates a given drug's data at the European level. This process results in one Community or European *marketing authorisation* that is valid throughout all EU Member States. The EMA administers the Centralised Procedure; however, the actual licence takes the form of a decision issued by the European Commission.

Regulation of Drugs in the US

The birth of FDA guardianship and the origins of drug and medical product regulation began with a large medical calamity¹². In 1937 over 100 people, mainly children, in the US died of diethylene glycol poisoning as a result of the use of a sulfanilamide elixir, which used the chemical as a solvent without any safety testing¹³. At that time, there were no required toxicities testing, scientific literature review, or animal experiments, and selling potentially toxic drugs was technically legal. In this case, product safety conflicted with another constraint- the desire for speedy market placement. This led to the introduction of the Federal Food, Drug and Cosmetic Act (FD&C) in 1938.

The second calamity that led to the expansion of medicines regulation far more than any event in history was the thalidomide disaster in the EU. Thalidomide was a sedative and hypnotic that first went on sale in Germany in 1956. Between 1958 and 1960 it was introduced in 46 different countries worldwide resulting in an estimated 10,000 babies being born with phocomelia. While this drug was not approved for sale in the US, the incident led the initiative for the FDA to regulate efficacy as well as safety for US bound drugs.

The FD&C Act defines drugs by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)].

The FDA's Center for Drug Evaluation and Research (CDER) job is to evaluate new drugs before they can be sold and to ensure that drugs marketed in the US are safe and effective.

The Route to Market for US Drugs

In the US, the FDA requires the following sequence of events prior to approving a drug; Preclinical Testing, *Investigational New Drug Applications* (IND), Phase I Clinical Trials, Phase II Clinical Trials, Phase III Clinical Trials, New Drug Application and Phase IV Studies.

During Preclinical testing a pharmaceutical company performs specific studies before the future drug is given to a human being. Laboratory and animal studies must be done to prove the biological activity of the drug against the targeted disease. The drug must also be evaluated for safety.

The pharmaceutical company **submits** an IND: with the FDA to begin testing the drug in people. The IND becomes effective if the FDA does not disapprove it within 30 days. The IND must include the following information: the results of previous experiments; how, where and by whom the new studies will be conducted; the chemical structure of the compound; how it is thought to work in the body; any toxic effects found in the animal studies; and how the compound is manufactured. The IND must also be reviewed and approved by the Institutional Review Board where the studies will be conducted.

Phase I Clinical Trial studies are usually the first tests of a drug under development in healthy volunteers. These studies involve about 20 to 80 volunteers. The tests determine a drug's safety profile, including the safe dosage range, plus how the drug is absorbed, distributed, metabolized and excreted, and the duration of its action. Phase I trials take on the average 1 year ¹⁴.

Phase II Clinical Trials are slightly larger studies that are done in patients with the disease for which the drug is intended. This phase is usually designed to identify what are the minimum and maximum dosages. The trials generally involve 100 to 300 volunteer patients and are controlled in design. They are done to assess the drug's effectiveness ¹⁴. Phase II typically takes about 2 years.

Phase III Clinical Trials are the definitive, large randomized trials that are submitted to the FDA in order to obtain approval of a drug. This phase examines the effectiveness as well as the safety of the new drug. Phase III trials usually involve 1,000 to 3,000 patients in clinics and hospitals. Patients are usually asked a list of possible side effects, often derived from what was observed in phase II studies. Patients are also free to report any other side effects that occur while they are on the new drug or the placebo. Phase III takes on the average 3 years.

Following the Phase III Clinical Trials, the drug manufacturer analyzes all the data from the studies and files a New Drug Application (NDA) with the FDA (provided the data appear to demonstrate the safety and effectiveness of the drug). The NDA contains all of the data gathered to date about the drug.

Phase IV is any organized collection of data from patients who are taking a drug that has already received approval from the FDA. In Phase IV studies, patients may check boxes on a list (as in phase III studies) or they may just report other symptoms. Phase IV studies are commonly called "post-marketing studies."

Although there are other routes that can expedite the process, this is the usual journey for a drug from invention to market in the U.S.

Summary

The overview of Medical device regulation demonstrated that it is a complex process. Part of the complexity can be attributed to the wide variety of items categorized as medical devices. Medical devices range from simple tools used during medical examinations such as tongue depressors and thermometers to high-tech life-saving implants like heart valves and coronary stents. Another contributing factor to its complexity is that despite having largely similar regulations for medical devices, the EU and US have adopted different approaches to oversight. The US market is controlled through a centralised agency, the FDA, whereas the EU is much more decentralised, monitored by CA-appointed Notified Bodies who have no legal powers and who are commercial organisations who charge fees to the manufacturers.

Drug regulations are also complex. Differences in how the regions approach drug regulation also add complexity. In the US once again the FDA is responsible; in Europe multiple agencies are involved: the European Medicines Agencies, Committee for drugs for human use (CHMP) and national health agencies. A good illustration of how the two regions differ in approach is the registration process: in the US there is one registration procedure; in Europe there are 3: centralised, decentralised and national.

The US and EU regulatory systems are under constant evaluation and scrutiny. They are an important element of any healthy, innovative medical technology ecosystem. They function as a tool for decreasing stakeholder uncertainty and ensuring public safety. Supportive regulations improve the investment climate in the industry by reducing related risks, and, hence, promoting innovation in the short run and better and cheaper healthcare in the long run. In the regional context, therefore, regulation

design can be a source of competitive advantage to a whole region in the international arena.

In conclusion this article aimed to provide an overview of the regulatory framework for medical device and drugs in the EU and US. The directives and federal laws that govern the approval of these products were presented. The review has demonstrated that the regulation of these products is extremely complex, which confirms the views of other commenters ^{15, 16}. Each jurisdiction has its own regulatory frameworks with different legislation. Furthermore there are a range of regulatory authorities involved which adds to the complexity of the process.

References

1. European Commission. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices L 169 *Official Journal of the European Community*. 1993(July):1-43.
2. European Commission. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices L 189. *Official Journal of the European Community*. 1990(July 20):17-36.
3. European Commission. Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices L 331. *Official Journal of the European Community*. 1998(December 7):1- 37.

4. European Commission. Council Directive 98/79/EC of 27 October 1998 concerning in vitro Diagnostic Medical Devices. In: Community OJotE, ed1993.
5. ISO. DIN EN ISO 14155 2012–01 Clinical investigation of medical devices for human subjects – Good clinical practice 2012.
6. Code of Federal Regulations. *Title 21, Parts 800-1299*. Vol U.S. Government Printing Office, Washington, DC,2002.
7. FDA. Federal Food, Drug & Cosmetic Act 21 *CFR* §3.2 (e). Vol 2006.
8. Maisel WH. Medical Device Regulation: An Introduction for the Practicing Physician. *Annals of Internal Medicine*. 2004;140(4):296-302.
9. Federal Drug Administration Modernization Act. *Public law*. 1997;105-115.
10. European Commission. 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to proprietary drugs. *Official Journal of the European Communities* 1965;22.
11. European Commission. Directive 2004/27/EC of the European Parliament and of the Council of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to drugs for human use (Text with EEA relevance) In: EC, ed2004.
12. Rago L, Santoso B. Drug regulation: history, present and future. *Drug Benefits and Risks: International Textbook of Clinical Pharmacology, revised 2nd edition*. 2008.
13. Ballentine C. Taste of Raspberries, Taste of Death The 1937 Elixir Sulfanilamide Incident. *FDA Consumer magazine* [1981; <http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm>]. Accessed 22 November 2012.

14. Food and Drug Association. The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective. 2012; <http://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm>. Accessed 30 April 2012.
15. Grignolo A. Collaboration and Convergence Bringing New Medicines to Global Markets in the 21st Century. *Therapeutic Innovation & Regulatory Science*. 2013; 47(1):8-15.
16. Hamrell MR. An overview of the US regulatory environment for drug-device and biologic-device combination products. *Drug Information Journal*. 2006; 40(1):23-32.

Class	Risk	Examples
Class I basic	Low Risk	Reusable surgical instrument Nonsterile gloves
Class I (sterile)	Low Risk	Sterile dressings, non-medicated Sterile gloves
Class I (with a measuring function)	Low Risk	Volumetric urine bag
Class IIa	Medium Risk	Surgical blades

		<i>A hypodermic needle</i> <i>Suction equipment</i>
Class IIb	Higher Risk	Ventilators, orthopaedic implants Radiotherapy equipments
Class III	Highest Risk	Prosthetic joints Coronary Stent

Table 1: E.U. Classification of Medical Devices and Examples of Devices in each Class

Class	Risk	Examples
Class I	Low Risk	Tongue Depressor Elastic Band Hospital beds
Class II	Medium Risk	Absorbable suture Blood pressure cuffs
Class III	Highest Risk	Implantable Pacemaker Pulse Generator Pacemaker Battery coronary stent

Table 1: U.S. Classification of Medical Devices and Examples of Devices in each Category