Regulatory strategy for an efficient launch of medical devices – a distinct focus on BRICS and MIST countries

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List of Abbreviations

AMDD	Agreement on Medical Device Directive
ANVISA	Agência Nacional de Vigilância Sanitária (Portuguese); English: Brazilian Health Surveillance Agency
AR	Authorized representative
ASEAN	Association of Southeast Asian Nations
BMG	Bundesministerium für Gesundheit (German); English: German Federal Ministry of Health
BRICS	Brazil, Russia, India, China, South Africa
CDRH	Center for Devices and Radiological Health
CDSCO	Central Drugs Standard Control Organization
CE	Conformité Européenne (French); English: European Conformity
CFDA	Chinese Food and Drug Administration
COFEPRIS	Comision Federal para Proteccion contra Riesgos Sanitarios (Spanish); English: Mexican Federal Commission for the Protection against Sanitary Risk
CSDT	Common Submission Dossier Template
EEC	European Economic Community
EU	European Union
FDA	Food and Drug Administration
GDP	Gross Domestic Product
GHTF	Global Harmonization Task Force on Medical Devices
HIV	Human Immunodeficiency Virus
i. e.	Id est (Latin); English: that means
IMDRF	International Medical Device Regulators Forum
IRB	Institutional Review Board
Ltd.	Limited
MCC	Medicines Control Council
MIST	Mexico, Indonesia, South Korea, Turkey
MS	Member state
PMA	Premarket approval
PMDA	Pharmaceutical and Medical Device Agency; Japanese Health Authority
SFDA	State Food and Drug Administration
STED	Summary of technical documentation
ToC	Table of Contents
US	United States

1 Introduction

1.1 Preface

During the last decades companies focused their business on major regions and countries, like the European Union (EU), the United States (US) and Japan. The saturation in these developed markets urges companies to expand to countries outside these regions. [1] This approach can also be observed in the pharmaceutical industry: By the year 2016, the worldwide pharmaceutical market will amount to 1.2 trillion US Dollars. While the share of the developed markets will decline to 57 percent of the total global spending - starting from 70 percent in the year 2009 - the emerging markets will increase by ten percent over the next years and thus account for about 30 percent. Doing business in emerging markets is therefore inevitable for pharmaceutical companies as these countries contribute tremendously to profitability and are even expected to carry industry growth over the next years. [2], [3]

Although in the year 2012 developed markets still dominated the medical devices sector by representing over 75 percent of total global sales, emerging countries are subject to much higher growth rates, which are two to five times as high as those in the developed markets, so that emerging markets are even considered as one of the most important driving forces for growth in the area of medical devices. [4] Emerging markets will even be responsible to balance the downward trend in some of the developed markets over the next years. [5]

Considering this outlook, it is important to understand these markets with regard to their local legislations for medical devices. While in the developed markets regulatory provisions and systems are well established in the area of medical devices, emerging markets are rather heterogeneous regarding medical device regulations and regulatory processes. It is the experience of the author that especially small- and medium-sized medical device companies without physical presence in the local market are particularly burdened by the rapidly changing diverse regulatory environment in these markets. In the area of medical device only little information, like published summaries, is available, and mostly not in English language at all.

Representative groups for emerging countries are BRICS and MIST. [6] These names stand for the first letter of each of their member states. BRICS, which

was first mentioned by a Goldman Sachs economist in 2003, covers Brazil, Russia, India, China and South Africa. [7] As demonstrated by Figure 1, the BRICS countries accounted for about 40 percent of the world's population in 2013, every individual representing a potential customer for the medical industry. [8]

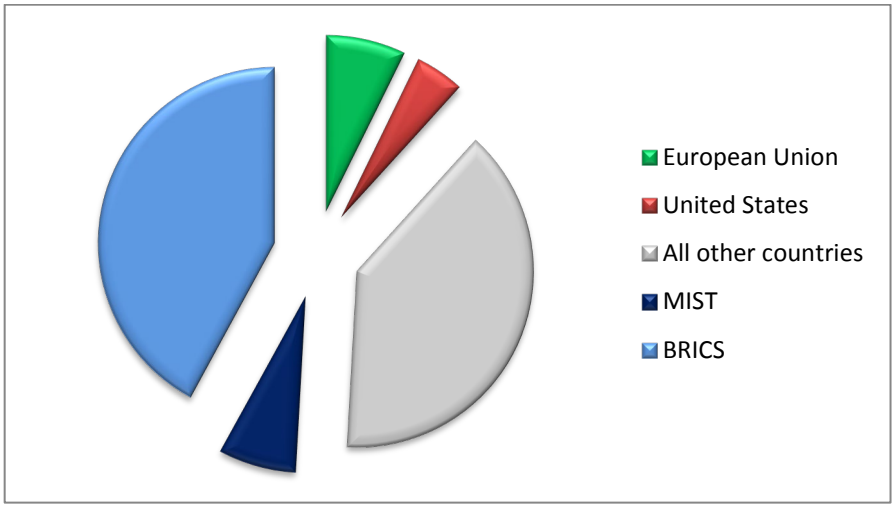

Figure 1 - Population per country / region (July 2013 estimate)
(According to Central Intelligence Agency [8])

As growth in the BRICS countries is slowing down [9], the founder of the BRIC term – which initially did not include South Africa – created another group of countries: MIST (also known as MIKT). This acronym stands for Mexico, Indonesia, (South) Korea and Turkey and one should not underestimated these countries' growth and power. [6] The size of the economy of the MIST nations more than doubled during the last ten years and even surpassed Germany in 2011. As illustrated by Figure 1 and Figure 2, the MIST countries do not reach the BRICS with regards to economic output or population, but each of the MIST countries constitutes at least 1 percent to the global Gross Domestic Product (GDP) and it is expected that this portion will even further increase during the upcoming decade. [10] Summing up the GDP of the BRICS and MIST countries, these nations would rank first (BRICS) and fourth (MIST) in the world. [8]

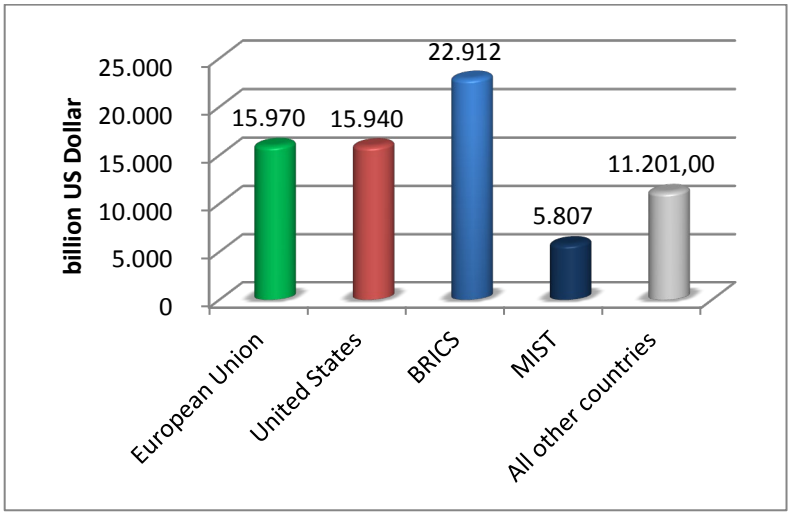

Figure 2 - Gross Domestic Product per country / region (2012 estimate)
(According to Central Intelligence Agency [8])

1.2 Research Objective and Scope

The objective of this Master Thesis is to define the regulatory environment for Medical Devices. This comprises regulatory provisions like registration requirements and processes, but also (not legally binding) guidelines as well as predictive approval timelines. The focus is on the EU, the US, BRICS and MIST countries (countries see below). With these facts a regulatory strategy will be developed and possible risk factors will be identified. The overall target of the regulatory strategy is to ensure an efficient launch of a medical device in the countries in scope by reducing time to submission and contribute to a rapid and cost-efficient market access.

The present work will mainly deal with the following two groups of emerging countries: The BRICS and MIST.

To establish a foundation of regulatory requirements for medical devices, the regulatory environment in the European Union and the United States will be outlined. These nations will remain the major markets for the years to come; therefore these countries will build the cornerstone of the regulatory strategy. The BRICS and MIST countries use these regions as their reference.

This work will only briefly touch on clinical investigations. Post-marketing activities, such as pharmacovigilance measures, variations and governmental control after placing a device on the market are also not in scope of this work, nor are medical devices for in-vitro diagnostics, active implantable medical

devices and ‘custom-made devices’, which are devices for an individual patient. Other major markets, like Japan, Canada, Australia and Switzerland, are also out of scope of this work.

1.3 Company and Product Scenario

Founded over 20 years ago, InnoContraception Ltd. is an innovative medical device manufacturer based in the United Kingdom. With annual global revenue of 250 Million US Dollar, it ranks among the top 100 medical device companies in the world. Its product portfolio consists of medical devices in the area of contraception offering innovative solutions in the women’s healthcare segment. The product in scope is a medical device which is implanted into the fallopian tubes, offering a surgery-free and hormone-free permanent birth control method. The product will undergo a safety and performance study in patients shortly and is planned to be launched in the year 2017. The following table presents the product’s characteristics.

Tradename	**FallopSafe**
Indication	Permanent birth control by bilateral occlusion of the fallopian tubes
Mode of action	Mechanical blockage of tubal lumen and tubal occlusion by tissue in-growth
Device components	Ergonomic handle Disposable catheter Implantable micro-insert
Manufacturing site	InnoContraception Ltd., United Kingdom

Table 1 - Product characteristics of case example

(Compiled by the author)

2 Medical Devices in the European Union and the United States

2.1 European Union

As an outcome of a harmonization relating to safety and performance of medical devices in the European Union (EU) about 20 years ago, medical devices are currently primarily regulated by three directives.

At present, the European regulatory medical device legislation is undergoing another revision as technological and scientific development over the last two decades is not reflected in the current regulatory framework. Additionally, the fact that directives have to be transferred into national law, lead to different interpretations and delayed implementations of these rules. Consequently, the European Commission published two proposals for new regulations in September 2012. They will replace the existing medical device directives after being discussed and amended by the European Parliament and the Council and will gradually come into force from probably 2017 onwards. They will be binding for all 32 participating countries: The 28 EU member states, the EFTA states Iceland, Norway and Liechtenstein as well as Turkey. [11], [12]

Medical device type	Current Directive	Future Regulation
Active implantable medical devices	90/385/EEC	Summarized in the 'Proposed Regulation'
Medical devices	93/42/EEC	
In vitro medical devices	89/79/EC	In vitro medical device regulation

Table 2 - Medical Device legislation European Union
(According to European Commission [11], [12])

It is planned to launch 'FallopSafe' in 2017. Consequently, all discussions in the present work are based on the proposed regulation for medical devices (hereinafter called the 'Proposed Regulation').

2.1.1 Key Players

Several entities play a central part in the registration of medical devices. Their roles mentioned in this chapter are restricted to regulatory activities required up to the time of launching a medical device and thus do not cover activities related to marketed devices.

Manufacturers

A manufacturer is any “natural or legal person who manufactures or fully refurbishes a device or has a device designed, manufactured or fully refurbished, and markets that device under his name or trademark.” [11] This definition implies that even if parts of the manufacturing chain are delegated to a third party, the manufacturer remains responsible for all obligations according to the ‘Proposed Regulation’ as long as the device is placed on the market under his name or trademark. [13] The obligations of a manufacturer vary according to the risk class of a device; i. e. requirements for high-risk devices are harsher than for low-risk devices. This is, for instance, reflected by the manufacturer’s responsibilities related to his quality management system. Detailed responsibilities of manufacturers are listed in Article 8 of the ‘Proposed Regulation’. Furthermore, a new requirement has been introduced with the ‘Proposed Regulation’. Accordingly, a manufacturer should appoint a 'qualified person' responsible for regulatory compliance, similar to the requirements in the EU legislation on medicinal products. [11]

Authorized representatives

The authorized representative (AR) can be “any natural or legal person established within the [European] Union who has received and accepted a written mandate from a manufacturer to act on his behalf”. The AR assumes specific tasks agreed with the manufacturer, his minimum responsibilities are reflected in paragraph 3 of Article 9. The appointment of an AR is inevitable for manufacturers not established in the European Union (EU), as he serves as the single point of contact for national authorities and notified bodies within the EU. [11]

Importers and Distributors

“Any natural or legal person established within the Union who places a device from a third country on the Union market” is considered an importer. In contrast, a distributor is the one who makes a device available on the market. General obligations of importers and distributors are covered by Article 11 and 12 of the ‘Proposed Regulation’. [11]

European Commission

This institution of the EU proposes and implements European laws. [14] The department responsible for medical devices is the Directorate General for Health and Consumers. Their aim is to ensure a high level of patient safety and promote innovation and competitiveness of the medical device industry by establishing a convergent regulatory framework. [15]

National competent authorities

National authorities are accountable for certain tasks related to the notified body, like the appointment of notified bodies and the supervision of their work [13] including the setup of the necessary procedures to do so, according to Article 28 of the ‘Proposed Regulation’. [11]

Notified bodies

The so-called ‘conformity assessment bodies’ are assigned and monitored by national authorities and carry out the conformity assessment. Today, there are about 80 notified bodies in Europe. [11] These privately held certification organizations are authorized to audit quality assurance systems of the manufacturers and check the devices’ compliance with applicable legislations. Notified bodies are also responsible to give advice on device classification and the applicable conformity assessment procedure. They conduct product and quality system evaluation, resulting in the notified body certificates, which are issued by the notified body as well. [13], [16] Depending on the class of a medical device, the level of notified body’s involvement varies, ranging from no involvement for devices of class I to a high involvement for class III devices. [13] The minimum requirements to be fulfilled by a notified body are covered by Annex VI of the ‘Proposed Regulation’. [11]

2.1.2 Product Categorization and Device Classification

The correct product categorization and medical device classification is essential to make sure the appropriate legislation is applied. Therefore, the first step is to verify that a product qualifies for a medical device as opposed to a medicinal product or cosmetic product. This categorization is determined by the following characteristics: While a medicinal product has a pharmacological, metabolic or immunological effect [17], the main purpose of a cosmetic product is mainly to

clean, perfume or correct body odors, change appearance, protect or keep the body in a good shape, while only being in contact with external parts of the human body, with teeth or the oral cavity. [18] In contrast, the main effect of a medical device is physical and includes mechanical action, physical barrier or replacement of and support to organs or body functions. [17] However, the purpose, like curing, preventing, diagnosing or treating a disease, is identical to a medicinal product.

The classification of medical devices is covered by Article 41 and Annex VII of the 'Proposed Regulation'. [19] It is a risk-based approach that considers the intended purpose and the vulnerability of the human body by applying a set of criteria, like the degree of invasiveness, the duration of contact with the body and whether the medical device is active or not. [20] Applying the 21 classification rules listed in Annex VII allocates a medical device to one of the four different classes. [19] Table 3 lists device classes and subclasses including their associated risk and some examples.

Class	Subclass	Risk	Examples
I	Basic	Low	Compression hosiery, eyeglasses
I	Sterile	Low	Sterile gloves
I	With measuring function	Low	Volumetric urine bag
IIa	Not applicable	Medium	Dental fillings, hearing aids
IIb	Not applicable	Higher	Condoms, X-ray machines
III	Not applicable	Highest	Hip prostheses, cardiac catheters

Table 3 - Classification of medical devices in the European Union
(According to Masterson and Cormican [13] and Bundesministerium für Gesundheit [21])

The existing classification rules lead to a precise classification for the majority of devices, but there may be some devices for which the classification is difficult. If several rules apply to one device, the rule that leads to the stricter classification is applied. In case of doubts, the notified body should be consulted and if no agreement can be reached, a decision will be taken by the competent authority in accordance with Article 41 of the 'Proposed Regulation'. [11], [20]

The implantable micro-insert 'FallopSafe' is used for contraception, poses a physical barrier and is thus considered as a medical device. The device class is determined by classification rule 14 which states that "devices used for contraception or the prevention of the transmission of sexually transmitted diseases are in class IIb, unless they are implantable or long term invasive

devices, in which case they are in **class III**." [11]

2.1.3 General Safety and Performance Requirements

Meeting the general safety and performance requirements according to Annex I of the 'Proposed Regulation' and demonstrating the device's conformity to these requirements is a must to place a device on the market. These requirements may be illustrated by a checklist in the technical documentation. [11] In the current Medical Device Directive these are called 'essential requirements'. [22]

General requirements

The device should perform according to the intended use with a focus on safety and health of patients and users. Thus, the manufacturer is accountable for risk identification, - reduction and - elimination. Providing appropriate training and information to users will support a positive benefit-risk ratio. [11]

Requirements regarding design and construction

This section defines chemical, physical and biological properties, for example the choice of the material and its compatibility with the human body and other substances with which they get into contact during their normal use. The design, manufacturing and packaging of the device should contribute to minimize any kind of risk, such as contaminants and residues to patients, risks related to particle properties and sizes used for the device as well as risks inducing infections to patients or microbial contamination. [11]

Requirements regarding the information supplied with the device.

Each medical device shall bear information to identify the device and its manufacturer and communicate information related to safety and performance to the user. This information can either be put on the device itself, on the packaging components or included in the instruction for use and needs to be appropriate according to the device class and the users. The scope of information to be provided on the label and in the instruction for use is defined in paragraphs 19.2 and 19.3 of Annex I. For devices of classes I and IIa it is not mandatory to have an instruction for use.

For implanted devices, like 'FallopSafe', patients should obtain essential information on the implant, like warnings and precautions to be taken and

information to ensure identification of the device. Furthermore, the Unique Device Identification (UDI) is a new aspect that has been added in Article 24 of the 'Proposed Regulation'. It is a unique number allocated to a medical device, with the following objectives: more efficient traceability of devices, easier recalls, enhancement of anti-counterfeiting and improving patient safety via a so-called UDI database, in which useful and relevant information are stored for each UDI. [11]

2.1.4 Technical Documentation

Annex II of the 'Proposed Regulation' defines the content of the technical documentation or the summary of technical documentation (STED). The structure of the technical documentation and the STED is illustrated in Figure 3.

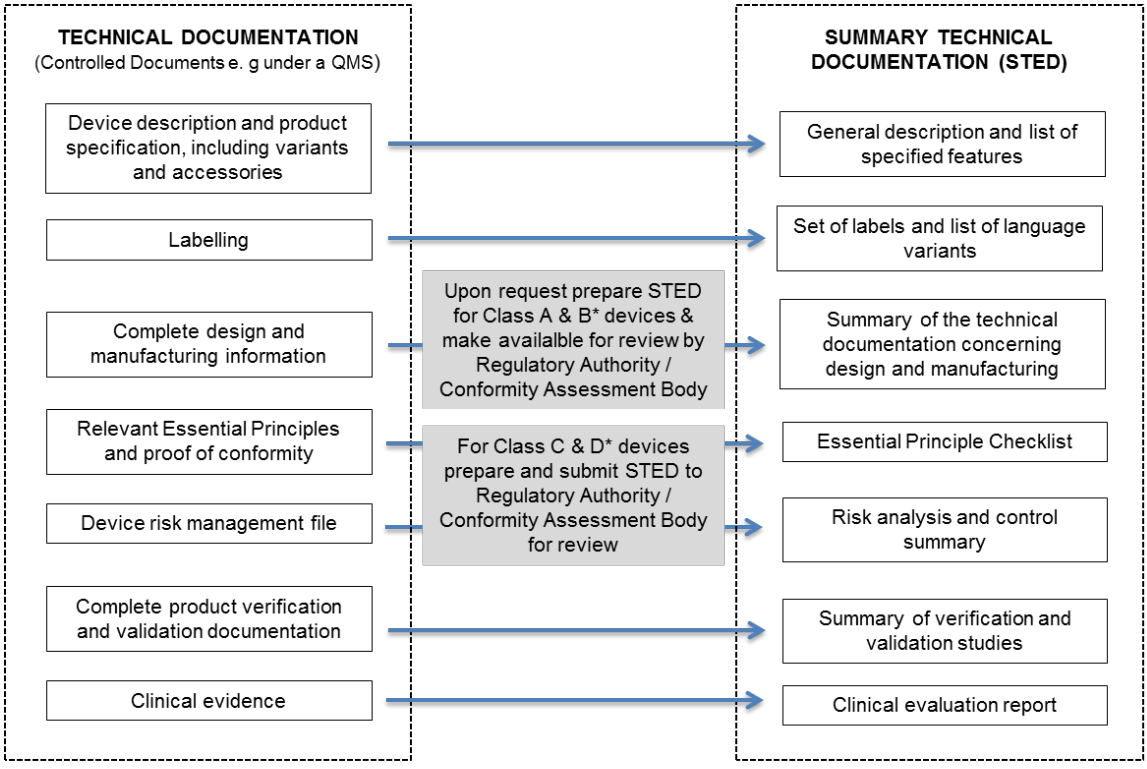

Figure 3 - Technical documentation and STED
(Global Harmonization Task Force [23])

For medical devices of classes I, IIa and IIb, the technical documentation is called 'technical file' while for class III devices it is named 'design dossier'. Design dossiers, which are more comprehensive, have to be proactively submitted to the notified body for review in order to get a CE-marking, whereas

technical files are kept for a possible review at the manufacturer or authorized representative. [24]

In case the technical documentation is very comprehensive and / or stored at various locations, the manufacturer needs to compile a STED from the technical documentation (Figure 3), submit the STED and, on request, provide the full technical documentation to the notified body. [11] [23] The content of the STED was defined by the Global Harmonization Task Force (GHTF) and can be found in Appendix 1. Just last year, the International Medical Device Regulators Forum (IMDRF) has created a proposal for the content of the technical documentation. It is important to know that not all modules are relevant for all countries and that some of the modules may contain regional elements in addition. [25] The IMDRF, which is the successor organization of the GHTF, is a group of medical device regulators from several countries worldwide, including Australia, Brazil, Canada, Europe, Japan and the United States. Amongst others, their aim is to globally standardize regulatory submissions for medical devices. [26]

2.1.5 Conformity Assessment

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

Article 42 of the ‘Proposed Regulation’ outlines the various conformity assessment procedures to be executed before putting the device on the market. They range from a declaration issued by the manufacturer himself without involving a third party to a conformity assessment based on full quality assurance and design dossier examination, involving a notified body. As summarized in Table 4, the ‘Proposed Regulation’ offers some alternatives to the manufacturer to undertake the conformity assessment procedure for medical devices. [11]

<table>
<tr><th>Class</th><th colspan="2">Assessment Procedure</th><th>Timelines</th></tr>
<tr><td></td><td>Option 1</td><td>Option 2</td><td></td></tr>
<tr><td>I</td><td colspan="2">Technical documentation (Annex II) and Declaration of Conformity (Annex III)</td><td>1 week
(non-sterile, non-measuring)[1]
3 – 5 months
(sterile or measuring)</td></tr>
<tr><td>IIa</td><td rowspan="2">Full quality assurance and assessment of design documentation within technical documentation (Annex VIII, except chapter II)</td><td>Technical documentation (Annex II) with conformity verification (Part A, section 7 or part B, section 8 of Annex X)</td><td>1 – 3 months</td></tr>
<tr><td>IIb</td><td rowspan="2">Type examination (Annex IX) with product conformity verification (Annex X)</td><td>2 – 6 months</td></tr>
<tr><td>III</td><td>Full quality assurance and design dossier examination (Annex VIII)</td><td>6 – 9 months</td></tr>
</table>

Table 4 - Conformity assessment procedures in the European Union
(According to European Commission [11] and Emergogroup [27])

A conformity assessment consists of two areas: On the one hand, this is the assessment of the device's technical documentation. After having demonstrated compliance with the provisions of the regulation, the notified body issues the EC Certificate(s). In the case of 'FallopSafe' this maybe either a 'Certificate on EC Type examination' (Annex IX of the 'Proposed Regulation') or a 'EC Design Examination Certificate' accompanied by a 'Quality System Approval Certificate' (Annex VIII of the 'Proposed Regulation'). Countries outside of the EU often use the general term 'EC Certificates' when referring to these kind of Certificates issued by the notified body.

On the other hand, this involves the assessment of the company's internal processes, referring to the quality management system, which all companies must have. For medium- and high-risk devices the notified bodies need to certify the manufacturers according to EN ISO 13485 "Medical devices - Quality management systems - Requirements for regulatory purposes". This is an

[1] Non-sterile, non-measuring class I devices can be self-certified by the manufacturer. Thus, the device can be placed on the European market one week after having submitted the necessary documentation to the competent authority, once the requirements of the regulation are fulfilled.

international standard published, among others, by the European Committee for Standardization. Compliance with this standard results in a so-called ISO Certificate. [28]

The technical documentation and the Declaration of Conformity according to Article 17 of the ‘Proposed Regulation’ are considered as key documents to prove compliance with the legal requirements for medical devices, because these two items are part of each of the above mentioned routes of conformity assessment, with a varying level of detail. Once the notified body has confirmed the product’s compliance, the manufacturer issues the Declaration of Conformity, confirming that compliance with the ‘General Safety and Performance Requirements’ of the ‘Proposed Regulation’ has been demonstrated. [11], [29] Appendix 3 of this work presents a template of the EC Declaration of Conformity. [24]

Finally, once a medical device has undergone an assessment and complies with the requirements of the applicable regulation, a CE marking (Figure 4) shall be affixed to the product according to Article 18 of the ‘Proposed Regulation’. [11] The CE marking indicates that a product qualifies to be freely distributed within the market of the European Economic Area (EEA), however it does not indicate that the origin of the product is in the EEA. [29]

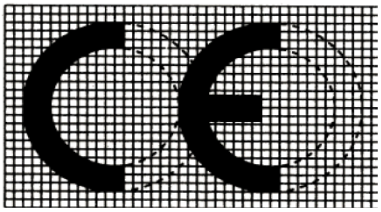

Figure 4 - CE marking of conformity
(European Commission [11])

2.1.6 Clinical Investigations and Clinical Evaluation

Clinical investigations are the equivalent to clinical trials for medicinal products. They are covered by Articles 50 to 60 and Annex XIV of the ‘Proposed Regulation’ and would require prior ethical and regulatory approval. The aims of these investigations are to verify that the design, manufacturing and packaging of a medical device is set up in such a way that the device is suitable for the specific purpose, or to verify intended benefits, or to determine any undesirable

effects. For implantable medical devices of class III, like ‘FallopSafe’, the performance of clinical investigations is mandatory to ensure high level safety and performance and demonstrate compliance with the general safety and performance requirements, unless it can be justified that existing clinical data provide reliable information. [11], [28] In contrast, clinical investigations are not obligatory for class I, IIa and IIb devices, but may also have to be performed depending on their clinical claims or results of the clinical evaluation. [30] However, the clinical evaluation covering assessment and analysis of clinical data is an integral part of the technical documentation and the manufacturer is obliged to conduct such an evaluation in accordance with Article 49 and part A of Annex XIII of the ‘Proposed Regulation’. This evaluation can be based on relevant scientific literature, results of clinical investigations or a combination of both. [11] The Guideline MEDDEV 2.7/4 is a guide for manufacturers and notified bodies for clinical investigations. [30]

2.1.7 Market Access

Preparations for market access comprise a wide range of company-internal activities as well as interactions with external parties. Company-internal activities include, but are not limited to, preparation of marketing and promotion material and activities, planning in the area of production and logistics as well as translation of labelling texts.

With the ‘Proposed Regulation’ a new requirement for implantable medical devices has been introduced. Consequently, for implantable medical devices like ‘FallopSafe’ the manufacturer is obliged to provide an implant card to patients who have been implanted with this device. This card should allow identification of the device, including UDI provide information on the expected lifetime of the device and inform patients and healthcare professionals about precautions and measures they can take concerning reciprocal effects with potential external influences or environmental conditions. [11]

Reimbursement and pricing of the device is an essential task towards market access. As with medicinal products, there is no common European approach for reimbursement of medical devices. By using Health Technology Assessments, national institutions of EU countries decide which products qualify for reimbursement and at what price. The applied criteria, methods and evidence

used to determine the extent of reimbursement vary. However, it is ensured that only medical devices which are clinically and economically effective are reimbursed. Consequently, the differences within the EU derive from local government health care systems and the decision which medical devices will qualify for reimbursement and which price is achieved is purely driven by governments, health insurance providers and available budgets. [31], [45]

2.1.8 Parallel imports

If a product is imported from one EU member state (MS) into another by a trader that is independent from the manufacturer (or the original authorization holder for medicinal products), and placed on the market in the destination MS, this is called ‘parallel import’. For medicinal products, this is legal if the imported product is “identical or sufficiently similar” to a product already authorized in the destination MS. [32] That is to say, even if a medicinal product is just imported into a country, it requires a marketing authorization in this country. This does not apply to medicinal products authorized via the European centralized procedure, as with this, the product is allowed to be marketed in all EU countries. The setting for medical devices in the EU is similar: Once a device bears a CE marking it can be distributed in the EU. With this, the foundation for parallel imports of medical devices is laid. Significantly different prices for similar products between EU MS, which result either from national regulations, like the different methods and criteria applied for Health Technology Assessment, or from the manufacturer’s' pricing strategy and policy encourage traders to buy products in one MS to a lower price and sell them in a MS in which the price is higher. By selling the product in the higher priced MS at a medium price, the trader makes profit and competition is stimulated. [33], [45] Specific regulations for parallel imports of medical devices in the EU do not exist.

2.2 United States of America[2]

In the United States, medical devices are regulated by different parts of the Code of Federal Regulations, Title 21. [34]

2.2.1 Key Players

The key players of a device registration in the United States (US) are similar to those of the European Union. Nonetheless, in the US there is only one principal regulatory body, the US Food and Drug Administration (FDA). [13] The US FDA regulates medical devices with its Center for Devices and Radiological Health (CDRH), whose responsibility is to control companies which manufacture, re-package, re-label, and / or import medical devices sold in the United States.
A foreign manufacturer will also need to designate a US agent, who will act as the local point of contact for the US FDA. Manufacturers, wholesale distributors and importers play a similar role in the US as in the EU. [34]

2.2.2 Device Classification

The US FDA classifies medical devices into three classes based on the risk the device poses to the patient and / or the user and the intended use. [35] Consequently, class I devices are considered non-life sustaining and class II devices are defined as more sophisticated and pose more risks than class I. [13] Class III devices support or sustain life and their failure would be life-threatening. They serve to prevent impairment of human health, or may present a potential risk of illness or injury. [36] Part 860 of 21 CFR provides detailed information on ‘medical device classification procedures’.
In practice, to determine the class of a medical device, the applicant can search in the device classification database, which was set up by the US FDA. About 1,700 different generic types of devices, grouped into 16 medical specialties have been defined. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device. [35]

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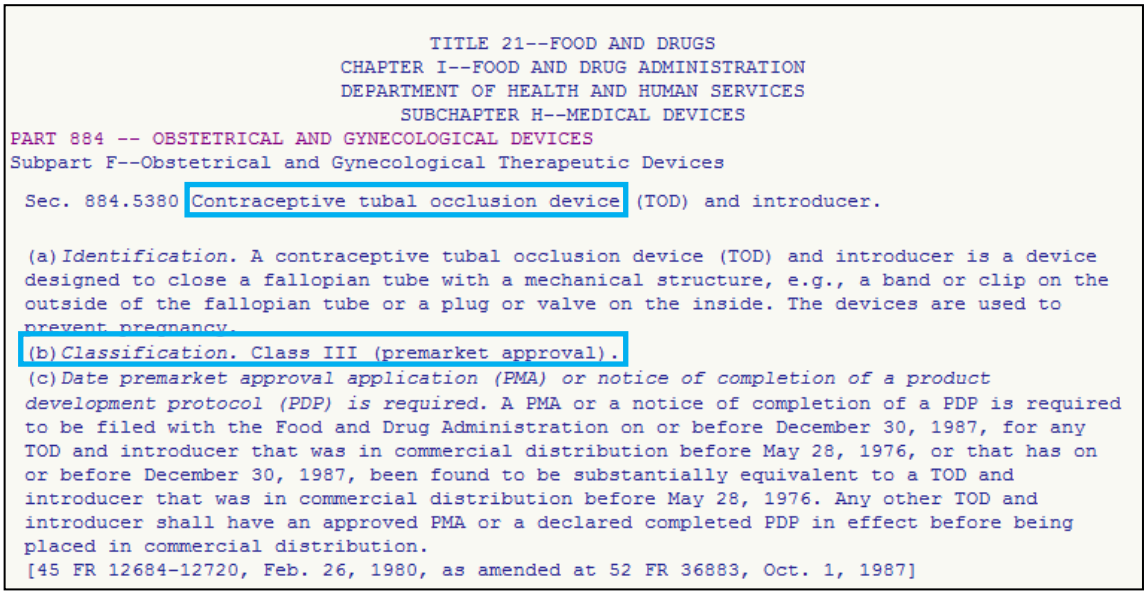
[2] For purpose of conciseness this chapter will only focus on the specifics of medical device registrations in the United States.

In the case of ‘FallopSafe’, the CFR defines that this devices is allocated to the panel ‘Obstetrical and Gynecological Devices’ (Figure 5). Apart from that, Section 860.93 of 21 CFR recommends that any implant is classified as class III. Hence, it is a class III device and requires premarket approval (PMA). [34]



TITLE 21--FOOD AND DRUGS
CHAPTER I--FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
SUBCHAPTER H--MEDICAL DEVICES
PART 884 -- OBSTETRICAL AND GYNECOLOGICAL DEVICES
Subpart F--Obstetrical and Gynecological Therapeutic Devices

Sec. 884.5380 Contraceptive tubal occlusion device (TOD) and introducer.

(a) *Identification.* A contraceptive tubal occlusion device (TOD) and introducer is a device designed to close a fallopian tube with a mechanical structure, e.g., a band or clip on the outside of the fallopian tube or a plug or valve on the inside. The devices are used to prevent pregnancy.
(b) *Classification.* Class III (premarket approval).
(c) *Date premarket approval application (PMA) or notice of completion of a product development protocol (PDP) is required.* A PMA or a notice of completion of a PDP is required to be filed with the Food and Drug Administration on or before December 30, 1987, for any TOD and introducer that was in commercial distribution before May 28, 1976, or that has on or before December 30, 1987, been found to be substantially equivalent to a TOD and introducer that was in commercial distribution before May 28, 1976. Any other TOD and introducer shall have an approved PMA or a declared completed PDP in effect before being placed in commercial distribution.
[45 FR 12684-12720, Feb. 26, 1980, as amended at 52 FR 36883, Oct. 1, 1987]

Figure 5 - Example for device classification according to CFR
(US FDA [34])

2.2.3 Regulatory Pathways for Device Registrations

The device classification determines the marketing authorization process, which can be a premarket notification (510(k) or PMN), a premarket approval (PMA) or an exemption from the aforementioned. These will be outlined in the following:

Premarket notification

A premarket notification, also known under the term ‘510(k)’, is relevant for devices, for which no exemption is defined in the regulation and which are not subject to a PMA. It is applicable to most of the class II devices. The aim of a premarket notification submission is to demonstrate that a device, which is planned to be marketed in the US, is ‘substantially equivalent’ to a so-called ‘predicate device’, a device already legally marketed. [38] Determining whether a device is ‘substantially equivalent’ involves an evaluation of the intended use and the technological characteristics. [34] However, it does not necessarily mean that the devices must be identical. Once the US FDA has confirmed that the device is substantially equivalent by sending a letter to the applicant, the

device is considered as FDA “cleared” and can be distributed on the US market. [38] 21 CFR, Part 807, Subpart E defines requirements, like content and format for a 510(k) application. [34]

Premarket approval

The premarket approval process (PMA), which applies to all medical devices of class III, involves a scientific and regulatory review evaluating safety and effectiveness of a medical device. The aim of the PMA is to demonstrate that there is sufficient scientific evidence to assure safety and effectiveness of the device. This type of a device marketing application is the strictest one [36] and is covered by 21 CFR, Part 814, Subpart B. A premarket approval process for a medical device runs through similar steps as the registration process for a medicinal product in the US: 45 days after submission of the application, the US FDA will notify the applicant on the acceptance for filing. The review starts and after involvement of the advisory committee’s recommendation, the process is finalized with an approval. [34]

These two procedures, 510(k) and PMA, imply that all devices, which cannot be considered as ‘substantially equivalent’ to a marketed device and which are not classified by the regulation, would have to go through a premarket approval procedure, like a class III device. For this case, the US FDA offers two further options: The so-called ‘De novo process’ and ‘Device exemptions’.

De Novo process

The ‘De Novo process’ is applicable to low risk devices. Devices, for which applicants of a 510(k) receive a ‘not substantially equivalent’ letter, would be placed into category of class III. In these cases the applicant can request a ‘De Novo classification’ of the device into class I or II within 30 days from the receipt of the letter. If the US FDA classifies the device into class I or II, the applicant will receive an approval to market the device and the device is then considered a ‘predicate device’ for other firms to submit a 510(k). If the result of the ‘De Novo process’ is that the device remains a class III device, the applicant has to submit a PMA. [37]

Table 5 shows the review timelines for the three mentioned procedures, 510(k), PMA and the ‘De Novo process’. However, the US FDA reveals on their website

that a PMA review usually takes longer and can take up to two years. [13], [36]

Procedure	Review timelines
510(k)	90 days
PMA	180 days
De Novo	60 days

Table 5 - Review timelines United States
(According to US FDA [34], [36])

Device Exemptions

Most devices of class I and some of the class II devices are exempted from the premarket notification requirements. Nevertheless, these devices are subject to other general control, e. g. all medical devices must be manufactured under a quality assurance program, suitable for the intended use and have an ‘establishment registration’ and device listing. [39]
In addition to this, there is also a device exemption for ‘humanitarian use devices’. This is similar to the principle of an orphan drug. If a device is intended to treat or diagnose a disease or condition that affects or is manifested in fewer than 4,000 patients in the US per year, the applicant needs to submit a PMA, but is exempted from some of the requirements. [40]

Establishment registration and device listing

The legislation 21 CFR Part 807 deals with the establishment registration. Accordingly, “owners or operators of place of business”, which are also called establishments or facilities, participating in the production and distribution of medical devices must register and list before exporting these devices to the US. [34]

2.2.4 Submission Requirements

All device classes are subject to ‘general controls’, which are considered to be the baseline requirements. For class II devices ‘special controls’ apply on top, while devices of class III ‘general and special controls’ are considered insufficient, which means that these class III products are subject to a ‘premarket approval’ (PMA). [35]
‘General controls’ include a quality assurance program in accordance with Good

Manufacturing Practices (GMP) in 21 CFR Part 820 ‘Quality System Regulation’. Furthermore devices need to be adequately packaged and properly labeled in accordance with the labeling regulations in 21 CFR Part 801 or 809 and they need a 510 (k) premarket notification.

‘Special controls’ comprise special labeling requirements, mandatory performance standards and the implementation of post market surveillance according to 21 CFR Part 800 to 898. [34], [41]

Section 807.87 ‘Information required in a premarket notification submission’ includes requirements for a 501(k) submission. The documentation must include performance data to confirm that the device is substantially equivalent to a predicate device. A PMA must include all requirements listed in 21 CFR, and Section 814.20 ‘Application’ to allow a scientific review ensuring safety and effectiveness of Class III devices. [34]

In 2003, the US FDA has set up a Summary of Technical Documentation (STED) Pilot Program, encouraging applicants to submit 510(k) and PMA applications in the STED format. [42]

2.2.5 Clinical Evaluation and Investigation

For some of the 510(k) submissions and for most of the PMA applications clinical investigations are required. This means that the manufacturer or agent will first have to apply for an Investigational Device Exemption (IDE). [43] Whether or not clinical studies are needed can be clarified in pre-submission meetings with the authority.

Just recently, the US FDA has issued a final rule amending the regulations on premarket approval for medical devices. Accordingly, the applicant will be required to include information on pediatric investigations in case the intended use of the respective device is to treat, diagnose or cure a disease or condition that is relevant to pediatric subpopulation. [44]

2.2.6 Market Access

In summary, to market a medical device, it is required to obtain market clearance from the US FDA, to label the device according to the Labelling Regulations and to register the establishment and list the type of device that is planned to be marketed. [43]

With regards to pricing and reimbursement, the responsibility in the US is with private as well as public payers. Thus, compared to the European Union, the process in the US is even less homogeneous due to the patchwork of public and private payers. Especially private payers may apply different processes and criteria to make their decision. Furthermore, in the US, complex and costly technology is not as much respected and reflected in the reimbursement price as in the European Union. [45]

3 Medical Devices in BRICS and MIST Countries

The regulatory environment in these two groups of emerging countries is very heterogeneous. Publicly accessible written legislations are limited, sometimes only available in local language and leave room for interpretation. To complement the information extracted from written guidelines, a questionnaire (Appendix 4) has been sent to local Regulatory Affairs Managers of a globally operating pharmaceutical company.

3.1 Brazil

Country fact sheet

Competent authority	Brazilian Health Surveillance Agency (ANVISA - Agência Nacional de Vigilância Sanitária)
Legal Basis	ANVISA Medical Device Resolution RDC Nº 185 from October, 2001
Device classification	Classes I, II, III, IV
Time to approval	85 – 210 days *(depending on device category and class)*

Table 6 - Country Fact Sheet Brazil

(According to ANVISA [46] and Country Questionnaire, 2014)

In Brazil, there are numerous regulations that govern the registration, import and distribution of medical devices. [47] According to the above mentioned main Medical Device Resolution, it is mandatory to register all medical devices, with a few exceptions, e. g. for those used in clinical trials or a new product presentation consisting of a set of devices that are already registered. [46] The competent authority ANVISA has a joint responsibility for medicinal products and medical devices. [Country Questionnaire, 2014] Following the principles of the major markets, devices are classified according to their potential intrinsic risk they might pose to a patient or operator. Annex II of the Medical Device Resolution contains 18 classification rules, which are identical to the current classification rules outlined in the European Medical Device Directive 93/42/EEC. [22], [46]

Required documentation

In order to register a medical device, the applicant is asked to submit the following documentation in Portuguese language to ANVISA. The

documentation varies depending on the device classification.

Documentation	Class I	Class II - IV
Sanitary surveillance fee: Proof of payment	☑	☑
Information identifying manufacturer / importer and the device acc. to Annex III.A, III.B and III.C of the resolution	☑	☑
Copy of authorization of manufacturer / exporter or importer*		☑
Proof of registration (certificate of free trade or equivalent document) issued by a an authority in manufacturing country or from a country in which the device is marketed*		☑
Proof of compliance with legal provisions of Technical Regulations and ANVISA medical device legislation	☑	☑

**for imported devices only*

Table 7 - Required submission documentation Brazil

(Compiled by the author)

The above mentioned Annexes III.A, III.B and III.C in Table 7 cover an application form in which the applicant provides information on the device manufacturer or importer, requirements on labels and instructions for use, which need to be submitted in Portuguese, and requirements of the technical report. [46]

In addition to the aforementioned submission documentation, the following documents are to be submitted with legalization by the Brazilian embassy:

- Document from the manufacturer authorizing the applicant to represent and market the device in Brazil, including a sworn Portuguese translation
- Good Manufacturing Practice (GMP) Certificate and Free Sales Certificate from country of origin
- Declaration explaining relationship between legal manufacturer and manufacturing site (if different)
- Declaration describing that the product is registered and commercialized in other countries

[Country Questionnaire, 2014]

As Brazil is one of the IMDRF members, the Summary of Technical Documentation (STED) also applies for medical device applications submitted to ANVISA. The submitted documentation is assessed by ANVISA, which will then issue a decision through publication in the Federal Government Gazette,

as it is also done for medicinal products. [46]

Regulatory Pathways

Depending on the device class, there are two different regulatory pathways: For low risk medical devices of class I and II a notification is sufficient while class III and IV devices need to be registered. [48]

Additionally, there is a distinction between the registration of equipment and material. Table 8 provides an overview on the timelines for the different device categories and classes.

Category	Class III, IV and II (with some exceptions)	Class I and II
Material	200 days	85 days
Equipment	120 days	120 days

Table 8 - Review timelines Brazil

(According to Country Questionnaire, 2014)

Country Specifics

ANVISA does not accept the European concept of CE Certification, which means that ANVISA performs an autonomous evaluation of a device. [Country Questionnaire, 2014] For medical devices of class III and IV, it is even required to submit a GMP Certificate from ANVISA. Thus, a GMP inspection of the manufacturing site is an integral part of a medical device registration process. [49]

Furthermore, only companies based in Brazil can apply for registration of a medical device, which implies that before submission contractual activities with local agents might become necessary in case the company does not have a subsidiary in Brazil. [50]

According to the interviewed local Regulatory Affairs Manager it is necessary to conduct local clinical studies to register medical devices in Brazil. There are no regulations for reimbursement of medical devices. [Country Questionnaire, 2014]

3.2 Russia

Country fact sheet

Competent authority	Federal Service for Control of Healthcare and Social Development (Roszdravnadzor)
Legal Basis	Main medical regulation - Government Regulation № 1416 from 27.12.2012 "Regulations for State registration of medical devices", and addendums: Government Regulations № 930 from 17.10.2013, № 615 from 19.06.2012 and № 352 from 06.05.2011.
Device classification	Classes I, IIa, IIb and III
Time to approval	50 – 110 days

Table 9 - Country Fact Sheet Russia

(According to Government of Russia [51] and Country Questionnaire, 2014)

For Russia, the main facts are summarized in Table 9. While the Russian Ministry of Health is in charge of medicinal products, medical devices are overseen by the Federal Service for Control of Healthcare and Social Development. [52] Only devices registered with this institution are allowed to be distributed in Russia. [53]

The classification of devices is identical to the legislation applicable for the European Union, [52] which is a result of the recently changed device legislation that was published at the end of 2012. It will come into force by mid 2014. [53]

Required Documentation

Article 9 and 10 of the main regulation define the content of an application. Besides general information on the device the following documentation must be submitted in Russian language:

- Power of attorney from manufacturer to his authorized representative
- Data on regulatory documentation for the medical device
- Technical documentation of the manufacturer*
- Operational documentation of the manufacturer for a medical product, including product label and instructions for use*
- Photographic image of the device
- Results of technical tests
- Results of toxicological studies of a device, which usage contemplates a

contact with the human body

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**as defined in Government Resolution No. 930* [51]

Regulatory Pathways

Similar to the US FDA, there are two ways to register a medical device in Russia. The first route is applicable for devices of class I and IIa, and which are equivalent to a device already registered in Russia with regards to classification, application and efficiency characteristics. For these so-called “analogue” devices, it is only required to demonstrates equivalence or compare the two devices by technical testing and a safety evaluation. The second route is relevant for class I and IIa devices without an equivalent device and all devices of class IIb and III. These must be tested for quality, efficacy and safety by local testing centers appointed by the Russian government. Tests that have been performed outside of Russia are not accepted, even if they were done in a similar way. [52]

Country Specifics

To register a medical device in Russia, an authorized manufacturer representative in Russian territory is required. However, one of the major hurdles to take for foreign manufacturers that plan to register a medical device in Russia is local testing. Even if a device possesses a European CE marking or a 510(k) clearance by US FDA, the Russian health authority will perform product testing to determine quality, safety and efficacy according to national standards. [52] This also implies the need for local clinical studies. [Country Questionnaire, 2014]

Another noteworthy obstacle is language. First of all, all aforementioned documents need to be provided in Russian language and, in case the source documents are available in different languages, certified translations need to be provided. [51] Furthermore, documents like power of attorney or ISO Certificates also need additional legalization with an Apostille. And lastly, Roszdravnadzor’s website and various regulations are only available in Russian, which makes it inevitable to involve a local expert. [52]

3.3 India

Country fact sheet

Competent authority	Central Drugs Standard Control Organization (CDSCO) (Medical Devices and Diagnostic Division)
Legal Basis	Drugs and Cosmetic Act, 1940
Device classification	Non-critical devices and Critical devices
Time to approval	6 - 9 months

Table 10 - Country Fact Sheet India

(According to CDSCO [54] and Thomson Reuters [55])

As listed in Table 10, in India, the CDSCO is the responsible drug regulatory authority for medical devices and medicinal products. However, currently medical devices are mostly unregulated. [55] Only a small number of devices specified as drugs are regulated in the Drugs and Cosmetic Act. Such devices are listed in the 'List of notified medical devices' issued by the Ministry of Health, such as drug eluting stents, orthopedic implants, intrauterine devices, condoms or surgical dresses. [56] Only these notified devices need to undergo a registration procedure. [54] Accordingly, devices are merely split into two risk categories: non-critical devices and critical devices. [55]

Required Documentation

To be allowed to import a medical device into India, several items need to be fulfilled: a Registration Certificate in Form 41, an Import License in Form 10 and Form 28 covering the registration of the manufacturing site. [54] There are several guidance documents that define the content of each item.

In order to get a registration certificate in Form 41, the following documentation is to be submitted:

- Cover letter and apostilled authorization letter
- Filled Form 40
- Filled Challan Form for the Payment of Fees
- Power of attorney (manufacturer's authorization to his agent in India)
- Wholesale license
- Notarized or apostilled Certificates: Free Sales Certificate, ISO 13485 Certificate, Full Quality Assurance Certificate, CE Design Examination Certificate

- Declaration of Conformity
- Inspection / Audit report
- Device and Plant Master File (according to the Annexes of the respective guidance document) [57]

Device manufacturers that submit an application to the Indian authority for the first time, need to submit form 45 (for a new drug license) to support the form 40 application. [27]

The application for an import license is driven by form 10 and is accompanied by the following documents:

- Cover letter and apostilled authorization letter
- Filled forms 8 (Application for license to import drugs) and 9 (Form of undertaking to accompany an application for an Import License)
- Wholesale and manufacturing license [58]

Form 28 needs to be submitted in order to get the registration of the manufacturing site. As this is purely related to the site and not to the device itself, it will not be further outlined in this work. The required documentation is listed in the ‘Guidance document on application for grant of Licence in Form-28 for manufacture of Medical Devices’. [59]

Regulatory Pathway

The above mentioned documentation needs to be submitted to the CDSC, whereas both, the registration certificates with Forms 41 and the import license with Form 10 can be applied in parallel. After a period of six to nine months, the agent obtains a registration certificate from the CDSCO. [27], [54]

Country Specifics

Only a few medical devices are subject to registration in India. To submit a medical device application, it is necessary to appoint an Indian authorized agent, who must have a valid wholesale license.

Integral parts of the registration process are the registration certificate, the import permit and the registration of the manufacturing site. Without one of these elements, a manufacturer will not be able to sell his device in India.

3.4 China

Country fact sheet

Competent authority	Chinese Food and Drug Administration (CFDA)
Legal Basis	Order No. 276 “Regulations for the Supervision and Administration of Medical Devices”
Device classification	Class I, II and III
Time to approval	50 working days (for testing) + 105 working days (for registration)

Table 11 - Country Fact Sheet China

(According to CFDA [60] and Country Questionnaire, 2014)

Besides its responsibility for medicinal products, the CFDA (formerly called State Food and Drug Administration (SFDA)) is responsible for all imported medical device registrations. (Table 11) For domestic medical devices the responsibility is split between the CFDA (for class III devices), provincial FDA (for class II devices) and cities’ FDA (for class I devices). [60]

The classification of devices is covered by SFDA Order No. 15 “Provisions for Medical Device Classification in China”. Applying the Chinese classification rules may lead to a different classification for the same device compared to the classification rules of major reference countries, like EU or US. [61] Devices for which safety and efficacy can be ensured through routine administration are defined as class I; In case further control is required to ensure their safety and efficacy they are considered as class II. Implantable, life-supporting or -sustaining devices as well as those posing a potential risk to human body are classified as a class III device and are consequently controlled more strictly. [60]

Required Documentation

According to SFDA Order No. 17 “Initial Registration of Imported Products (Medical Devices)” the applicant needs to submit a Chinese registration standard dossier composed of following crucial documentation for registration:

- Filled application form
- Certificate from country of origin to authorize the manufacturer to produce and distribute the device (equivalent to manufacturing license)
- Document proving that medical device is approved in the country of

origin, e. g. 501(k) ... or PMA from US FDA and CE Certificate from EU. If these documents are not available a Free Sales Certificate needs to be submitted. In case the product is not authorized in the country of origin, special requirements apply as outlined in Article 3 of Order No. 17.

- Technical specifications and test methods which refer to the requirements for safety and technical functions of the device to be registered
- Instruction for use
- Test report not older than one year at time of application by a device control institute recognized by the SFDA (only relevant for devices of class II and III)
- Clinical trial report
- Declaration issued by the manufacturer certifying that the quality of the product to be registered in China is identical to that of the product marketed in the country of origin (Product Quality Guarantee)
- Letter of Authorization to representative agency for product registration
- Self-declaration to guarantee the authentication of the submitted documentation (Truth and Accuracy Statement)
- Operational Manual of the device as defined in Article 5 of Order No. 17.

These documents need to be either provided as an original, sealed by the manufacturer or legalized by a notary. [62]

Regulatory Pathways

Chinese FDA distinguishes between imported and domestic medical devices. [63] The following information is related to imported medical devices.

The first steps before starting the device registration are to apply for the classification review to CFDA and receive the classification confirmation, to appoint a local agent, to conduct clinical trials, if needed, and to perform product testing by an institution accredited by CFDA for class II and III devices. [64] With these prerequisites the registration procedure, which consists of following steps (Table 12), can be started:

Step	Regulatory activity	Duration (Working days)
1	Submission of specifications and test methods for verification and approval to the Medical Device Control Institute	5 - 10
2	Verification and approval of specifications and test methods by the Medical Device Control Institute; Submission of specifications, test methods and other required data to this institute for testing	45
3	Test reports are provided by the institute to the applicant; submission of all required registration documents to CFDA	-
4	Format review by CFDA	5
5	Evaluation of registration data	60
6	Administration examination	10
7	Approval of the application	10
8	Issue of approval	10
9	Issue of Import Medical Device License	10

Table 12 - Registration procedure China
(According to Thomson Reuters [63])

For device of classes II and III, product testing is a major milestone towards the registration. In these cases, additional documentation and materials need to be submitted in addition to the Chinese registration standard dossier. [63] Depending on whether the medical device is a domestic one or from a foreign country and depending on the device class, the review timelines may vary. Time to conduct clinical trials and type tests is different for foreign medical devices than for domestic ones. The authority is free to involve external experts into the technical evaluation of devices, for which the time would be added to the usual timelines outlined in Table 12. [65]

Foreign manufacturers must submit a notarized as ISO 13485 Certificate or an equivalent quality system certificate according to an international standard. [27]

Country Specifics

For devices of class II and III, data on clinical trials needs to be submitted. [60] The requirements of a clinical trial vary depending on whether the device is new and has not yet been marketed and those for which a similar product is already available on the market. [66]

Moreover, it is required to perform local testing for devices of class II and III,

which involves submission of a quality registration standard together with device samples for testing by a local agent. The local agent has a similar function as the EU authorized representative. [60]

With regards to labelling, the CFDA has some special requirements according to which it is not allowed to use specific terminologies, like ‘promise for cure’ or ‘immediate effect’ or expressions that are suggestive of getting ill or worsening of the health condition in case the product is not used. [67]

In China, there is no specific regulation that controls pricing or stipulates reimbursement of medical devices. However, it is necessary to get a confirmation of the price from China Nation Development and Reform Commission or the corresponding provincial affiliate. The pricing is calculated by production cost, reasonable sales and reasonable profits. In case doctors suggest a certain therapy, that necessitate the use of a medical device, the costs associated with this therapy are usually reimbursed by the China basic medical care insurance, as long as the patient is a member of this insurance. [63]

3.5 South Africa

Country fact sheet

Competent authority	Medicines Control Council (MCC)
Legal Basis	*None*
Device classification	*Not defined*
Time to approval	1 month (listing only)

Table 13 - Country Fact Sheet South Africa
(According to Country Questionnaire, 2014)

As of today, South Africa does not have a legal basis for the registration of medical devices (Table 13). A draft version of a medical device regulation is currently being finalized for implementation by the new combined regulatory body for pharmaceuticals and medical devices, called South African Health Products Regulatory Authority (SAHPRA). Up to now, only electronic medical devices are subject to registration, all others only require to be listed into a register. [68], [Country Questionnaire, 2014]

Required Documentation

According to the draft regulation, the following will have to be submitted to the Council after having paid the application fee:

- samples of the medical device for testing purposes,
- brochures or technical documentation,
- any other material related to the medical device. [69]

Regulatory Pathway

The draft regulation stipulates two assessment procedures: An abbreviated assessment process for devices already registered in a country outside of South Africa and a “normal” assessment procedure for all new devices. [69]

Country Specifics

For a sophisticated country like South Africa, it is surprising that no comprehensive legislation exists for medical devices. However, it is strongly recommended that the devices either bear a CE marking or are approved by the US FDA. [Country Questionnaire, 2014]

As stated in the draft regulation, manufacturers, importers or distributors of medical devices in South Africa need a license, which is issued by the Council once compliance to Good Manufacturing Practice and export / import practice according to the draft regulation is confirmed. Furthermore, the manufacturer needs to appoint an authorized representative in South Africa, similar to the EU concept. [69]

3.6 Mexico

Country fact sheet

Competent authority	COFEPRIS (Comision Federal para Proteccion contra Riesgos Sanitarios)
Legal Basis	Criteria for the classification of medical devices based on their level of health risk, dated 26 August 2010
Device classification	Class Ia, I, II and III
Time to approval	3 – 15 months

Table 14 - Country Fact Sheet Mexico

(According to COFEPRIS [70] and Country Questionnaire, 2014)

In Mexico, medical devices are managed by COFEPRIS, which is also in charge of medicinal products. [Country Questionnaire, 2014] The device

classification is similar to that in the EU. Moreover, there is a ‘list of deregulated devices’, i.e. devices that do not need any kind of registration and a ‘list of class Ia devices’ with very low risk devices that only need to be notified to COFEPRIS before being placed on the market. [71]

Required Documentation

The scope of the submission documentation depends on the regulatory pathway. For class Ia devices, it is only required to submit an application form, accompanied by the proof of payment, documentation of the Mexican Registration Holder, compliant labelling and instruction for use. For device applications of all other classes, it is also required to submit a document confirming approval in the country of origin in the form of a Free Sales Certificate, information on the product, including materials information, description of manufacturing process, finalized testing and, if applicable, sterility information, expiry date and clinical data. If the device is submitted under the equivalency agreement with US, Canada or Japan, the applicant must proof compliance with the equivalency requirements. [71] In all cases, the documentation needs to be in Spanish language.

Regulatory Pathway

There are different options to register a medical device in Mexico:

Equivalency review

If a device is already registered with US FDA, Health Canada or Japanese Pharmaceutical and Medical Device Agency (PMDA), the so-called ‘expedited process’ can be applied. [72]

As specified in Table 15 the difference to a standard process is not considerably reflected in the review timelines.

Third party review

There are certain “third party companies” which have been authorized by COFEPRIS to perform reviews for medical devices of class I, II and III. With this, the review period can be reduced by about half of the time. However, this option is not available for the equivalency review.

Standard review

In case a device is neither submitted via the “equivalency” route nor through the

third party review process, the device registration is subject to the standard review process. [27] Review timelines for these submission pathways are shown in Table 15.

	Class Ia	Class I	Class II	Class III
Equivalency Review	3 – 4 months	6 – 12 months	6 – 12 months	6 – 12 months
Standard process	3 – 4 months	4 – 10 months	6 – 16 months	6 – 16 months
Third party review	3 – 4 months	4 months	4 months	4 months

Table 15 - Review timelines Mexico
(According to Emergogroup [27])

Country Specifics

In Mexico it is necessary to appoint a Mexican Registration Holder, who will then coordinate the submission and maintenance of a medical device application. [27]

Another special element in the registration procedure is the ‘equivalency agreement’ with the United States, Canada and Japan. This enables a manufacturer to refer to an existing registration in one of these countries and allows for a smooth and quicker review compared to the standard process. [72] However, the review timelines from submission to approval deviate between theoretic information and practical experience. While the theoretic timelines are outlined in Table 16, hands-on experience resulted in review times of 18 to 24 months. [27], [Country questionnaire, 2014]

For class III devices, submission of clinical trials is required, but they do not need to include Mexican population. [27]

3.7 Indonesia

Country fact sheet

Competent authority	Ministry of Health (KEMKES)
Legal Basis	Decree 1190/MENKES/PER/VIII/2010 on marketing authorization of medical devices and household devices, dated 23 August 2010
Device classification	Class I, IIa, IIb and III
Time to approval	6 – 9 months

Table 16 - Country Fact Sheet Indonesia (today)

(According to Country Questionnaire, 2014 and Ministry of Health Indonesia [73])

Before being allowed to distribute medical devices in Indonesia, it is required to obtain a marketing authorization from the Ministry of Health (KEMKES), as opposed to the National Agency of Drug and Food Control which is responsible for medicinal products. [73], [Country Questionnaire, 2014]

Indonesia is a member of the Association of Southeast Asian Nations (ASEAN), which has drafted an Agreement on Medical Device Directive (AMDD) with the aim to harmonize device classification and requirements among the member states. The agreement is not a legally binding document, but will serve as a model for its member states. Implementation is expected by December 2014 and it is expected that Indonesia will adopt it as well. [74], [75] Therefore, the following information will be based on the AMDD. Devices can be assigned to class A, B, C or D according to their associated risk by applying the classification rules laid down in Annex 2 and Annex 3 of the AMDD. [75]

All in all, the AMDD is similar to the current EU Directive 93/42/EEC with regards to content and structure.

Required Documentation

According to the AMDD, the following technical documentation needs to be submitted for a medical device application, meeting the essential principles of safety and performance listed in Annex 1.

- ASEAN Common Submission Dossier Template (CSDT) (according to Annex 4 of the agreement) with depth and detail depending on the device classification and complexity
- Post Marketing Alerts System (PMAS) Requirements (according to

Article 12 and Annex 5 of the agreement) and

- Product Owner‘s or Physical Manufacturer‘s Declaration of Conformity (as outlined in Annex 6 of the agreement) covering ISO 13485 as one of the requirements in the area of international standards [74], [75]

According to a Local Regulatory Affairs Manager known by the author, the CSDT format has already been implemented for submissions of devices in Indonesia. [Country Questionnaire, 2014]

For imported medicinal products, additional administrative documents, like a legalized letter of authorization to the local agent and a Free Sales Certificate will also be needed for submission. [74]

Regulatory Pathway

The AMMD implements conformity assessments similar to the principles in the EU. Hence, the medical device is assessed by the regulatory authority, or an appointed body recognized by the authority, for conformity and compliance with the requirements laid down in the AMDD. Each member state will then have to establish an appropriate system for the conformity assessment of medical devices. [75]

With the current Indonesian medical device legislation, there are different routes for the registration of domestic devices as opposed to imported devices, which basically differ in the scope of documentation to be submitted. [74] The timelines for approval depend on the device class (Table 17). However, according to practical experience it takes about 6 to 9 months to obtain a medical device registration. [Country Questionnaire, 2014]

Class	Working days
I	30
IIa and II b	60
III	90

Table 17 - Review timelines Indonesia

(According to Country Questionnaire, 2014)

Country Specifics

Medical device registrations can only be done by a local agent or distributor. [73] Clinical trials are only needed for medical devices of class III, however there is no need for local clinical studies as international clinical studies are

accepted. A guideline on clinical trials for medical devices is currently not in place. [74], [Country Questionnaire, 2014]

At present, there is no specific regulation regarding pricing and reimbursement for medical devices. [Country Questionnaire, 2014]

3.8 South Korea

Country fact sheet

Competent authority	Ministry of Food and Drug Safety (MFDS)
Legal Basis	Major regulation: Medical Device Act (dated 28 November 28 2010)
Device classification	Grade (Class) 1, 2, 3 and 4
Time to approval	2 weeks - 10 months (depending on the classification)

Table 18 - Country Fact Sheet South Korea

(According to MFDS [76] and Country Questionnaire, 2014)

In Korea, medical devices are handled by the Ministry of Food and Drug Safety (MFDS), which is also responsible for medicinal products (Table 18). With regards to medical devices, the MFDS is supported by designated institutions, which are involved in the assessment of class 2 devices. The legal framework for medical devices is comprehensive and consists of numerous regulations. As for other countries, medical devices are sub-divided into four classes according to their related risk. [Country Questionnaire, 2014] The MFDS has issued 'Regulations for Product Classification of Medical Device and Class by Product' which includes a comprehensive list of medical devices and their assigned risk class. [77] As opposed to other countries, the device is not classified by the manufacturer himself, but by a MFDS commissioner. [76]

Required Documentation

For devices of class 1 only basic information need to be submitted in line with the pre-market notification, while for classes 2, 3 and 4 devices a technical file has to be prepared. [27]

Chapter 2 of the Korean 'Regulations for Reviewing Technical Document, etc. of Medical Device' elaborately lists the technical documentation required for submission of a so-called 'request for review'. [78]

For class 2 devices and some of the devices of class 3, the technical documentation is similar to the European documentation or the documents

required for a 510(k) submission in the US. Most of the class 3 devices and devices assigned to class 4 need a so-called ‘Safety and Efficacy Review’ (SER) in addition. This is similar to the US PMA. [79]
However, since January 2014 the STED format became mandatory for class 4 devices. For devices of class 1 to 3, the STED format is accepted, but not obligatory. [80], [Country Questionnaire, 2014]

Regulatory Pathway

The timelines for reviewing a device application are listed in Table 19.

Class	Time
1	2 – 4 weeks
2	4 – 6 months
3	6 – 10 months
4	6 – 10 months

Table 19 - Review timelines South Korea
(According to Country Questionnaire, 2014)

Medical devices of class 1 must only go through a pre-market notification process. For devices of class 2 to 4 the submission procedure consists of several steps, starting with the submission of the technical file and the so-called safety and efficacy review, if needed, followed by type testing which is done by an independent laboratory. Compliance with Korean industrial and International standards is a prerequisite. Usually, testing according to ISO or another International standard may be accepted. [27], [78]
The assessment of the technical documentation for class 2 device is done by designated institutions which are certified by the MFDS. The latter is performing the assessment of the technical documentation for class 3 and 4 medical devices. [Country Questionnaire, 2014]

Country Specifics

To manage a device registration with the MFDS, support of a local office is inevitable. On the one hand a local Korean license holder is needed and on the other hand all submitted documents must be in Korean language. [27] Another prerequisite before a foreign manufacturer can register a medical device is to apply for an import business license from MFDS and an import product license for each device. [76], [80] The manufacturer also needs to comply with the

Korean Good Manufacturing Practice quality system, which may involve an on-site inspection of the foreign manufacturing facilities. [27]

For devices of class 2, 3 and 4 clinical data are required, but may be accepted from other markets, so whether local clinical studies are needed is decided case by case. [27], [Country Questionnaire, 2014]

Reimbursement is an essential step for marketing a medical device in Korea. Thirty days after the device approval, the license holder must submit an application to the Health Insurance Review Agency, which will then set the reimbursement price for the medical device. With this, the device is set on a reimbursement list of the National Health Insurance system. Only with this listing, the device will be used by hospitals. Devices that are sold “over the counter” do not need to be included on the list. [81]

3.9 Turkey

Country fact sheet

Competent authority	Ministry of Health / Turkish Drugs and Medical Devices Institution
Legal Basis	European Legislation
Device classification	Class I, IIa, IIb and III
Time to approval	3 months

Table 20 - Country Fact Sheet Turkey

(According to Country Questionnaire, 2014)

In Turkey, medical devices as well as medicinal products are handled by Turkish Ministry of Health. (Table 20) Their medical device regulation was first published in 2002. The current medical device regulation is based on the European legislation. [Country Questionnaire, 2014] Turkey is one of the 32 participating countries of the ‘Proposed Regulation’. Thus, based on an international agreement between the European Economic Community and Turkey dated back to the year 1963, the requirements of this ‘Proposed Regulation’ apply to Turkey as well. [11]

Therefore, the classification of devices, the required documentation and the approval process itself is aligned with the European legislation.

According to the local Regulatory Affairs Manager known by the author, medical devices need to be registered into the National Databank of Pharmaceuticals

and Medical Device of Turkey, called TITUBB, which is operated by the Turkish Ministry of Health. It is split into two phases:

- **Document approval:** All documents need to be uploaded to the national data bank system and then they are submitted as hard copy followed by a document approval.
- **Product approval:** Secondly, a product registration is done in TITUBB and a hard-copy notification is sent to the applicant confirming that the product registration is completed.

[Country Questionnaire, 2014]

This product approval is a prerequisite for reimbursement of medical device. [82]

Country Specifics

Although Turkey has adopted the EU Medical Device Directives and is even listed as one of the participating countries in the ‘Proposed Regulation’, a Turkish authorized representative will be needed for submission of a medical device in Turkey. Conducting local clinical studies is not required. [Country Questionnaire, 2014]

4 Global Regulatory Strategy for Medical Devices

A strategy is defined as a method or plan to lead to a desired achievement of a goal or solution to a problem. A global regulatory strategy for medical devices involves consideration of numerous elements, such as content and timing of submission, regulatory risks, health authority meetings and so on.

Pursuing the objective

For the mentioned case example with the product ‘FallopSafe’, outlined in chapter 1.3 the aim is to pave the way from a regulatory perspective succeeding in a quickest possible launch of this medical device. The overall objective of a strategy should get attention throughout the entire development phase of a device and may need to be modified as new information or data become available. The same applies to the regulatory probability of success per country, which should be calculated right at the beginning and continuously updated.

Preliminary considerations

The device needs to be classified very early in the development process in order to determine the path forward. All countries classify devices according to their associated risk for patients and health care professionals. As ‘FallopSafe’ is a device to be permanently implanted into the human body, it is assumed to be allocated to the highest device class in all countries in scope.

In close alignment with the Business and Marketing function, the list of countries in which the device is going to be registered should be agreed upon. Only countries with a certain market potential should be considered.

Building relationships

During the development and registration process several parties need to interact with each other.

Local agents play a key role in medical device registrations in all considered countries. On the one hand they are required as per the regulations; on the other hand these local entities help to overcome barriers for foreign companies, like language issues and the know-how of local requirements and processes. Often websites and local regulations are only available in local language and local agents can benefit from participation in local regulatory or industry

networks. However, this implies to set up contracts or agreements with agents well in advance. Within the company it is necessary to set up a global project team with experts from all relevant functions, like clinical, analytical and technology development, regulatory affairs, market access, including representatives from local affiliates, if available. The involvement of external consultants may be required as well.

Up-front communication with all involved parties about the upcoming submissions of clinical investigation applications or registration submissions is a key to success.

Furthermore, health authority meetings can help to understand agency thinking and clarify requirements. Last, but not least, such meetings help to establish a relationship and create a trustful basis for future communication.

Clinical Investigations

It is required to plan clinical investigations early in the development plan according to the countries' requirements. The participating countries and the required number of patients according to local regulations need to be considered. While Brazil and Russia certainly will have to be included into the global clinical investigation, the participation of China and South Korea will have to be discussed with the health authorities case-by-case.

Content of submission

As the requirements for medical devices are not homogeneous throughout the countries, different types of dossiers will have to be prepared. The technical file as a 'design dossier' and the STED will cover the requirements of the majority of countries and will support seeking international regulatory approval. However, some countries will have to incorporate country-specific documentation resulting in national 'customized' dossier versions. The ASEAN Common Submission Dossier Template (CSDT) will be needed for submission in Indonesia and can also be used for other countries belonging to ASEAN.

Besides the technical documentation, there are also administrative documents that need to be prepared. Each country has unique regulatory requirements that need to be considered when setting up the project plan. These requirements include Free Sales Certificates (FSC), ISO Certificates, EC Certificates and

Declarations of Conformity, power of attorney, local application forms and country-specific declarations. The FSC is a key document in the registration process of medical devices in emerging markets. Figure 6 illustrates which countries need a FSC for submission and which countries do not require a FSC. For countries located in the middle of the two circles a FSC may be need in certain situations or may at least be supportive for the submission procedure.
Legalization by a notary or embassy and translations to different local languages may pose additional administrative hurdles. Therefore, sufficient time needs to be planned for these activities.

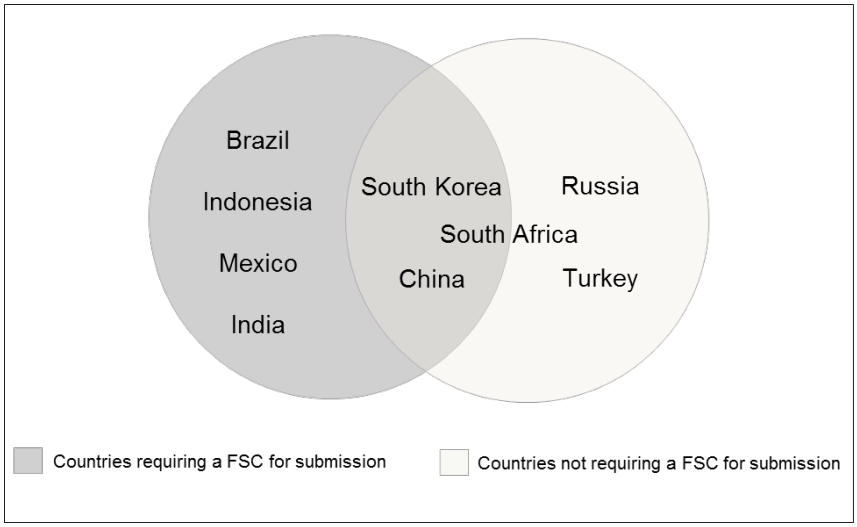

Figure 6 - Need for Free Sales Certificates
(According to Country Questionnaire, 2014 and Emergogroup [83])

Timing of submission

In the EU, US, Russia, China, South Africa, South Korea and Turkey the authorities perform an independent review of the medical device application. These countries can start with their submissions whenever the documentation has been compiled for submission by the manufacturer. The other countries in scope of this work require an approval in a so-called reference country before submission. Usually this reference country is the US or EU, but it may also be written in the legislation that the reference country is the country of origin, which is the country in which the medical device is manufactured. While Brazil, Mexico and Indonesia require approval in the country of origin, India also accepts an approval from the US FDA, even if the device is not manufactured in the US.
Considering the need for translations, legalizations and preparation of local

documents, Figure 7 presents a potential submission and approval plan. The numbers in the timeline stand for the months and the lengths of the bars indicate the review time from submission to approval. Looking at EU and Brazil, this implies that from submission to approval in the EU it would take nine months. As Brazil is one of the countries in which submission can only be done once the medical device is approved in the country of origin, Brazil could start submission right after this. As it is required to submit legalized documents in Brazil and some of these documents, like the ISO or EC Certificates will only become available after approval in the EU, Brazil will be able to submit about ten months after EU submission. Approval in Brazil can then be expected another seven months later (or 17 months after initial submission in the EU).

The proposed submission strategy divides all countries into three different groups or batches. The first batch of countries is highlighted in light blue. This batch comprises the countries in which submission is started off. These are mainly the developed regions EU and US, which also serve as reference countries to many of the BRICS and MIST countries. Countries like Turkey and South Africa also belong to this first batch of countries, as Turkey can be served with the same documentation as EU and for South Africa it is currently only required to list the device without any additional documentation.

Right after this, the submissions in the second batch of countries, highlighted in light yellow, are prepared. This preparation mainly involves the translation and legalization of documents. Theoretically and according to their medical device legislation, these countries could submit together with the developed regions, but due to capacity constraints, companies often decide to submit time-delayed.

The third batch of countries, represented in grey color, summarizes those countries that need to wait for an approval in one of the reference countries.

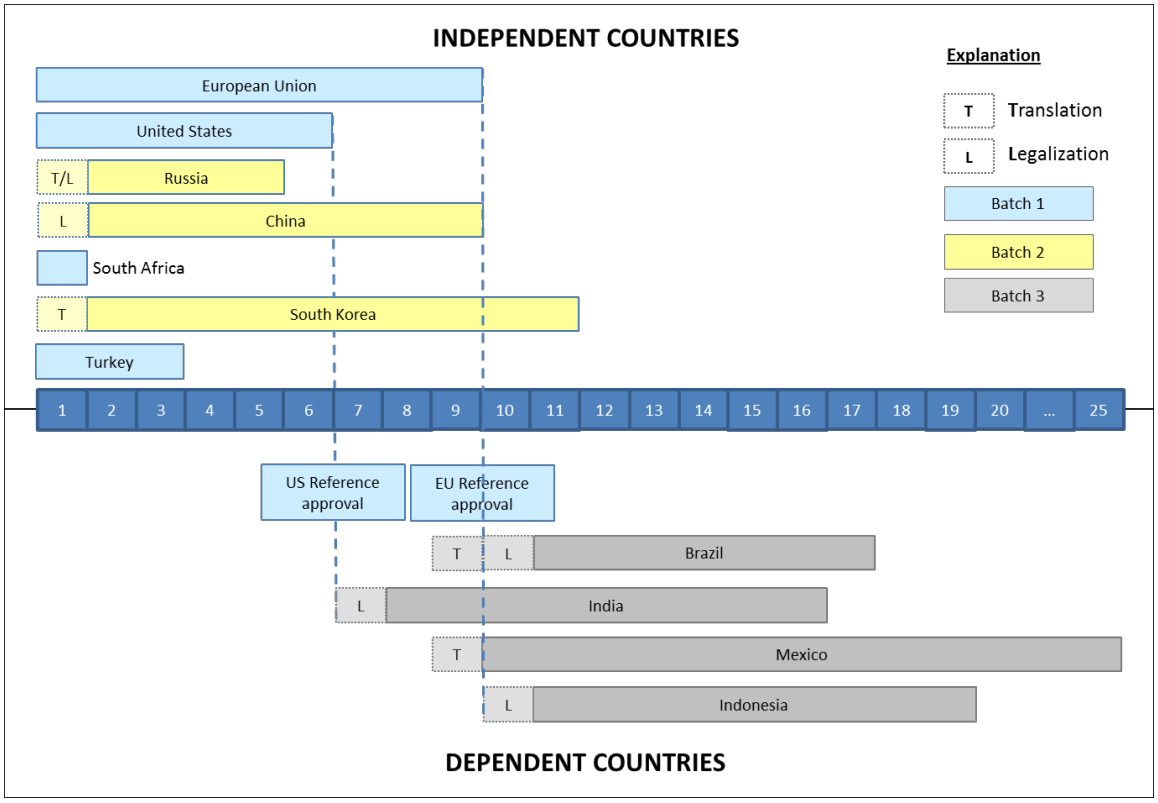

Figure 7 - Global submission and approval plan

(Compiled by the author)

Having a plan

To have a clearly defined project plan throughout the entire lifetime of the project is inevitable. The submission and approval timeline paired with a check list of requirements, documentation and activities as presented in Table 21 will help to set up and follow the global regulatory strategy.

Item	EU / US	BRICS / MIST
Confirmed list of countries	☑	☑
Agreements / Contracts with agent	☑ (AR)	☑
Clinical Investigation Applications	☑	☑
Health Authority Meetings / Scientific Advice	☑	☑
Set up project plan (submission timelines)	☑	☑
Design dossier	☑	☑
STED	☑	☑
CSDT		☑
National dossier versions / modules		☑
Collect additional data / documents / information for technical dossier, e. g. raw data		☑
Need for separate company registration	☑ (US)	☑
Stability studies	☑ (CZ I, II)	☑ (CZ III, IV)
Check possibility of common make-ups for shared articles	☑	☑
ISO 13485 Certificate(s)	☑	☑
Notified Body's EC Certificates (Certificate on EC Type Examination / EC Design Examination Certificate + Quality System Approval Certificate)	☑	☑
Manufacturer's EC Declaration of Conformity	☑	☑
Free Sales Certificate(s)		☑
Translation of documents	☑	☑
Legalization of documents		☑
On-site inspections (Brazil, Korea)	☑	☑
Mock-ups (instruction for use, labels, folding box)	☑	☑
Photographs of the device		☑
Product samples (illustration or testing)		☑
Technology transfer for local testing Russia, China)		☑
Country-specific declarations		☑
Local application forms		☑
Power of attorney		☑

Table 21 - Checklist for medical device registration

(Compiled by the author)

Accelerating registration and launch

Already during the planning phase of a project, the time to approval and launch can be indirectly influenced. Making use of a consultant who is familiar with medical device registrations in the respective countries will help not to overlook any important aspects.

Once a project plan is set up, resources according to identified peak times can be organized, which leads to the next element that can accelerate the registration. Additional resources, either budget or people to support the project will help to manage high workload during the preparation and submission phase.

A proactive compilation of the documentation is another tool to speed up with the registration procedure. This can be achieved by starting translation of documents once they are available, rather than waiting until all documents are available and by a rolling compilation of the dossiers.

Last but not least, synergies should be created whenever possible. A comparison of the requirements of major markets of EU and US with those of the emerging markets (Table 21) highlights that several documents from EU and US submission can be recycled for submissions in the emerging markets.

In the end, the acceleration of the registration process will either be at the cost of budget or at the cost of people.

Imponderabilities

The regulatory environment for medical devices in emerging markets is still in transformation. Depending on the scope and time, changes in the legislation may have disastrous consequences for a product that is currently being developed. If, for example, a local health authority defines that local clinical studies are needed and this country was not considered in the clinical development plan, this would result in a considerable delay of submission and additional budget for local clinical studies.

The presented submission and approval plan indicates that preparation and submission in several countries will overlap. During this “peak time” resources will not be sufficient to accomplish all submissions.

Working with a local agent may also pose some uncertainties. In case the manufacturer is far away from the local agent, there is a lack of control and its

loyalty towards the manufacturer is difficult to judge.

After having performed all submissions, health authorities (HA) may send list of questions. The point in time for these HA questions is unpredictable and does not allow for a proper resource planning.

Minimizing risks through co-operation

As a medium-sized company, it might be an option to cooperate with a partner to manage a complex submission. This can be either a global medical device consultant group or a globally operating pharmaceutical company taking advantage of their physical presence, established authority relationships and regulatory knowhow in the countries.

Setting up a regulatory intelligence process with a focus on device regulations in the countries in scope will support involved parties to become aware of changes in the regulations and react to these changes as fast as possible. This implies that may also need to be adjusted over time.

5 Conclusion

5.1 Findings

The right classification of a device is the foundation of the entire regulatory strategy and should take place very early in the development. It determines the applicable conformity assessment procedure and thus, the scope of documentation and the need for clinical trials. [11]

All considered countries classify devices according to their associated risk for patients and health care professionals. Applying the rules of various countries, very similar results are achieved, but possible differences should be considered. Differences also occur in the extent and amount of the documentation. BRICS and MIST countries often need additional administrative documentation including legalization and translations, which are usually not required for submissions in the EU and US. Nevertheless, possible creation of synergies should be considered early in the development phase of a device, so that the documentation is set up in such a way that the requirements of as many countries as possible can be fulfilled.

In comparison to medicinal products, the registration process of medical devices in BRICS and MIST countries is much more unregulated. This unpredictable regulatory environment makes it difficult for manufacturers to understand timelines and identify hurdles, risks and potential delays. On the one hand, this implies a constant need for gathering for information and updates on the local regulations. On the other hand, this also leaves room for creativity and opportunity for faster timelines. In any case, early planning and preparation of the submissions is essential for an efficient registration and launch process and a good planning will pay off.

Additionally, the time to approval may heavily depend on the exchange and communication between the health authority or notified body and agent or manufacturing company.

Last but not least, experience plays a major role in the area of medical devices in these countries as regulations are often not explicit enough and timelines vary in theory and practice. Thus, having a partner who understands the regulatory and competitive environment of the local market is highly recommended and can be the difference between success and failure.

Consequently, the set-up of a global strategy may vary, depending on the device type, its risks, its intended use and its performance claims, and may need to be adjusted over time.

All in all, successful accomplishment of a global regulatory strategy for medical devices is strongly driven by capacity and financial and human resources, be it external consultants who support the planning phase, the submission preparation and submission of the medical device application, or subject matter experts who will be needed to answer the list of questions from health authorities.

At the end, the manufacturer can make the decision whether or not a product is introduced into a specific local market. This is usually done by weighing ethical aspects, like supplying patients with innovative products, against economic aspects, such as the fact if profits will pay-off for the investments for the development and regulatory activities in a country. Chapters 3 and 4 of this work provide helpful information to support a manufacturer in decision-making in this area.

5.2 Outlook

The implementation of the ‘Proposed Regulation’ in the European Union will harmonize medical device registrations throughout Europe. It is anticipated that further harmonization efforts throughout the world will take place. The International Medical Device Regulators Forum (IMDRF) is a good start but seems to be still in its infancy. The extension of the IMDRF will drive the acceptance of the STED format for medical device dossiers worldwide and could make the need for different dossier types redundant. Just now, the IMDRF membership of China and Russia is currently being confirmed. [26]

It can be expected that regulations in emerging markets, including BRICS and MIST countries, will become more mature within the next years, but will also bring about an increasing level of requirements. The same holds true for legislation regarding pricing and reimbursement, which is currently even less controlled than the medical device registration.

It will not be possible to completely harmonize medical device regulations all over the world, however creating synergies on the authorities’ and manufacturers’ side by mutual recognition of assessments like in the EU or the

ASEAN CSDT is desirable and will further contribute to an efficient registration and launch of medical devices throughout the world.

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Appendix 1 Content of the STED

(see also chapter 2.1.4, page 10 and the following)

Device Description and Product Specification, including Variants and Accessories

- Device Description
  - a general description including its intended use/purpose
  - the intended patient population and medical condition to be diagnosed and/or treated and other considerations such as patient selection criteria
  - principles of operation
  - risk class and applicable classification rule according to the regulation
  - an explanation of any novel features
  - a description of accessories, other medical devices and other products that are not medical devices, which are intended to be used in combination with it
  - a description or complete list of the various configurations/variants of the device that will be made available
  - a general description of the key functional elements, e. g. its parts/components (including software if appropriate), its formulation, its composition, its functionality
  - a description of the materials incorporated into key functional elements and those making either direct contact with a human body or indirect contact with the body
- Product Specification
  - List of features, dimensions and performance attributes, its variants and accessories that would appear in the product specification made available to the end user
- Reference to similar and previous generations of the device
  - Overview of the manufacturer's previous generation(s) of the device and / or similar devices available on the local and international markets

Labelling

- Labels on the device and its packaging
- Instructions for use
- Promotional material

Design and Manufacturing Information

- Device Design

- High-level overview of the design stages (e. g. in form of a flow chart)

- Manufacturing Processes
  - High-level overview of the manufacturing processes (e. g. in form of a process flow chart showing an overview of production, assembly, final product testing and packaging)
- Design and Manufacturing Sites
  - Identify the sites where the aforementioned activities are performed

Essential Principles (EP) Checklist including cross-references to the location in the technical documentation / STED

- EP checklist that identifies
  - the Essential Principles
  - whether each Essential Principle applies to the device
  - the method(s) used to demonstrate conformity with each EP that applies
  - a reference for the method(s) employed (e. g. standard)
  - the precise identity of the controlled document(s) that offers evidence of conformity with each method used
- Methods used to demonstrate conformity may include the following:
  - conformity with recognized or other standards
  - conformity with a commonly accepted industry test method(s)
  - conformity with an in-house test method(s)
  - the evaluation of pre-clinical and clinical evidence
  - comparison to a similar device already available on the market

Risk Analysis and Control Summary

- summary of risks identified in the risk analysis process and how these risks are controlled to an acceptable level

Product Verification and Validation

- General
- Biocompatibility
- Medicinal Substances
- Biological Safety
- Sterilization
- Software Verification and Validation
- Animal Studies
- Clinical Evidence

Appendix 2 Content of the technical documentation

(according to IMDRF, see chapter 2.1.4, page 10)

Chapter 1: Regional Administrative	
Module	**Heading**
M1.1	Cover letter
M1.2	Submission ToC
M1.3	Application Form / Administrative Information
M1.4	Listing of Device Models / Variants
M1.5	Quality Management System, Full Quality System or Product Certification Certificate
M1.6	Free Sale Certificate
M1.7	User Fees
M1.8	Pre-Submission Correspondence and Previous Regulator Interactions
M1.9	Acceptance for Review Checklist
M1.10	Statements/Certifications/Declarations of Conformity
M1.11	Performance and Voluntary Standard
M1.12	Environmental Assessment
M1.13	ClinicalTrials.gov
M1.14	Indications for Use Statement with Rx and OTC designation Enclosure
M1.15	Truthful and Accurate Statement
M1.16	Class III Summary and Certification
M1.17	Declaration of Conformity
M1.18	Letters of Reference for Master Files
M1.19	Letter of Authorization

Chapter 2: Submission Context	
Module	**Heading**
M2.1	Chapter ToC
M2.2	General Summary of Submission
M2.3	Summary and Certifications for Premarket Submissions
M2.4	Device Description
M2.5	Comprehensive Device Description & Principle of Operation
M2.6	Description of Packaging

M2.7	History of Development
M2.8	Reference and Comparison to Similar and/or Previous Generations of the Device
M2.9	Indications for Use and/or Intended Use and Contraindications
M2.10	Intended Use / Intended Purpose / Intended User
M2.11	Intended Environment for use
M2.12	Indications for Use
M2.13	Pediatric Use
M2.14	Contraindications For Use
M2.15	Essential Principles (EP) Checklist
M2.16	Global Market History
M2.17	Global Market History
M2.18	Global Incident Reports and Recalls
M2.19	Incident Rate of Incident Reports and Recalls
M2.20	Substantial Equivalence Discussion
M2.21	Other Submission Context Information

Chapter 3: Non-clinical evidence	
Module	**Heading**
M3.1	Chapter ToC
M3.2	Risk Management
M3.3	Standards
M3.4	List of Standards
M3.5	Declaration and/or Certification of Conformity
M3.6	Non-clinical Studies
M3.7	Physical and Mechanical Characterization
M3.8	[Study description, study identifier, date of initiation]
M3.9	Summary
M3.10	Full Report
M3.11	Chemical Characterization
M3.12	[Study description, study identifier, date of initiation]
M3.13	Summary
M3.14	Full Report
M3.15	Electrical Safety and Electromagnetic Compatibility
M3.16	[Study description, study identifier, date of initiation]
M3.17	Summary

M3.18	Full Report
M3.19	Radiation Safety
M3.20	[Study description, study identifier, date of initiation]
M3.21	Summary
M3.22	Full Report
M3.23	Software/Firmware
M3.24	[Study description, study identifier, date of initiation]
M3.25	Summary
M3.26	Full Report
M3.27	Biocompatibility and Toxicology Evaluation
M3.28	[Study description, study identifier, date of initiation]
M3.29	Summary
M3.30	Full Report
M3.31	Immunological Testing
M3.32	[Study description, study identifier, date of initiation]
M3.33	Summary
M3.34	Full Report
M3.35	Pyrogenicity Evaluation
M3.36	[Study description, study identifier, date of initiation]
M3.37	Summary
M3.38	Full Report
M3.39	Biological Safety
M3.40	[Study description, study identifier, date of initiation]
M3.41	Summary
M3.42	Full Report
M3.43	Sterilization Validation
M3.44	End-User Sterilization
M3.45	[Study description, study identifier, date of initiation]
M3.46	Summary
M3.47	Full Report
M3.48	Manufacturer Sterilization
M3.49	[Study description, study identifier, date of initiation]
M3.50	Summary
M3.51	Full Report
M3.52	Residual Toxicity
M3.53	[Study description, study identifier, date of initiation]

M3.54	Summary
M3.55	Full Report
M3.56	Cleaning and Disinfection Validation
M3.57	[Study description, study identifier, date of initiation]
M3.58	Summary
M3.59	Full Report
M3.60	Animal Testing
M3.61	[Study description, study identifier, date of initiation]
M3.62	Summary
M3.63	Full Report
M3.64	Human Factors/Usability
M3.65	[Study description, study identifier, date of initiation]
M3.66	Summary
M3.67	Full Report
M3.68	Non-clinical Bibliography
M3.69	Safety and Performance Studies to Support Combination Products
M3.70	[Study description, study identifier, date of initiation]
M3.71	Summary
M3.72	Full Report
M3.73	Expiration Period and Package
M3.74	Expiration Period of the Product
M3.75	[Study description, study identifier, date of initiation]
M3.76	Summary
M3.77	Full Report
M3.78	Package Validation
M3.79	[Study description, study identifier, date of initiation]
M3.80	Summary
M3.81	Full Report
M3.82	Other non-clinical Evidence
M3.83	[Study description, study identifier, date of initiation]
M3.84	Summary
M3.85	Full Report

Chapter 4: Clinical Evidence

Module	Heading
4.1	Chapter ToC

4.2	Overall Clinical Evidence Summary
4.3	Device Specific Clinical Trials
4.4	[Trial description, protocol #, date of initiation]
4.5	Clinical Trial Synopsis
4.6	Clinical Trial Report
4.7	Clinical Trial Data
4.8	Clinical Literature Review and Other Reasonable Known Information
4.9	Other Clinical Evidence
4.10	[Study description, study identifier, date of initiation]
4.11	Summary
4.12	Full Report
4.13	IRB Approved Informed Consent Forms
4.14	Investigators Sites and IRB contact information
4.15	Location of clinical study records

Chapter 5: Labelling & Promotional Material

Module	Heading
5.1	Chapter ToC
5.2	Product/Package Labels, Package Insert/Instructions for Use
5.3	e-labelling
5.4	Physician Labelling
5.5	Patient Labelling
5.6	Technical/Operators Manual
5.7	Patient File Stickers/Cards and Implant Registration Cards
5.8	Product Brochures

Chapter 6A: Quality Management System Procedures

Module	Heading
6A.1	Cover Letter
6A.2	Chapter ToC
6A.3	Administrative
6A.4	Product Descriptive Information
6A.5	General Manufacturing Information
6A.6	Required Forms
6A.7	Quality management system procedures

6A.8	Management responsibilities procedures
6A.9	Resource management procedures
6A.10	Product realization procedures
6A.11	Design and development procedures
6A.12	Purchasing procedures
6A.13	Production and service controls procedures
6A.14	Control of monitoring and measuring devices procedures
6A.15	QMS measurement, analysis and improvement procedures
6A.16	Other Quality System Procedures Information

Chapter 6: Quality Management System Device Specific Information

Module	Heading
6B.1	Chapter ToC
6B.2	Quality management system information
6B.3	Management responsibilities information
6B.4	Resource management information
6B.5	Product realization information
6B.6	Device Specific Quality Plan
6B.7	Design and development information
6B.8	Purchasing information
6B.9	Production and service controls information
6B.10	Control of monitoring and measuring devices information
6B.11	QMS measurement, analysis and improvement information
6B.12	Other Device Specific Quality Management System Information
6B.13	Quality Information to support combination products

Appendix 3

Template EC Declaration of Conformity

Issued and signed by the manufacturer

DECLARATION OF CONFORMITY	
MANUFACTURER:	*NAME AND ADDRESS*
EUROPEAN REPRESENTATIVE:	*NAME AND ADDRESS*
PRODUCT:	*NAME, TYPE AND/OR MODEL*
CLASSIFICATION:	*CLASS, RULE ACCORDING TO ANNEX IX OF THE MDD* (NOT MANDATORY BUT RECOMMENDABLE)
CONFORMITY ASSESSMENT ROUTE:	*ANNEX APPLIED*
WE HEREWITH DECLARE THAT THE ABOVE MENTIONED PRODUCTS MEET THE PROVISIONS OF THE COUNCIL DIRECTIVE 93/42/EEC FOR MEDICAL DEVICES. ALL SUPPORTING DOCUMENTATION IS RETAINED UNDER THE PREMISES OF THE MANUFACTURER.	
STANDARDS APPLIED:	*LIST OF (HARMONIZED) STANDARDS FOR WHICH DOCUMENTED EVIDENCE OF COMPLIANCE CAN BE PROVIDED*
NOTIFIED BODY:	*NAME, ADDRESS AND IDENTIFICATION NUMBER*
(EC) CERTIFICATE(S):	*EC CERTIFICATE(S) NUMBER(S)*
START OF CE-MARKING:	*DATE, LOT NUMBER OR SERIAL NUMBER OF FIRST CE-MARKING*
PLACE, DATE OF ISSUE:	*CITY, DATE*
SIGNATURE:	_____ *NAME* *POSITION*

Appendix 4

Results from country questionnaire

Questions sent to local Regulatory Affairs Managers of the respective countries:

1. What is the name of competent authority responsible for medical devices?
2. Do you have a medical device regulation?
3. Do you involve other organizations / institutions (like the notified bodies in the European Union) into the assessment of medical devices? If yes, which are they?
4. How long does the health authority review from submission to approval for a medical device take? (Please separate by different medical device classes, if applicable.)
5. Is there any special format (e. g. STED format) for the submission dossier? Which essential documentation do you need to submit for a medical device?
6. Do you require local clinical studies for submission of a medical device?
7. Are there any regulations regarding pricing and reimbursement?
8. Does your authority accept a CE mark?
9. Would you need a Free Sales Certificate for submission of a medical device in your country?
10. Would you rank your medical device regulations rather EU or US-oriented? (1 equals EU regulation; 5 equals US regulation)

Question	BRAZIL
1	Brazilian Health Surveillance Agency (ANVISA - Agência Nacional de Vigilância Sanitária)
2	Yes
3	No
4	**Equipment registration:** class III, IV and class II (some exceptions) - 120 days **Equipment simplified registration:** class I and II - 120 days Material registration: class III, IV and class II (some exceptions) - 200 days **Material simplified registration:** class I and II - 85 days
5	No. - Copy of legal document in which the product manufacturer authorizes the applicant to represent and market your product in the country, together with sworn translation into Portuguese (legalized)

	- Report of Certificates of Good Manufacturing or Certificate of Free Trade in the country of origin (legalized) - Declaration explaining the relationship between legal manufacturer and manufacturing site (legalized) - Declaration describing that the product is registered and commercialized in other countries (legalized) - Labeling/ artwork in Portuguese <u>Technical Report</u> - Detailed description of the medical device, including the fundamentals of their operation and their actions, their content or composition when applicable, and list of accessories to integrate the product - Indication, purpose or use for which the medical device is intended, as indicated by the manufacturer - Precautions, restrictions, warnings, special cautions and clarifications on the use of medical devices, as well as storage and transport - Presentations of medical devices - Flowchart containing the steps of the productive manufacturing process of the medical device, with a brief description of each step of the process, until the finished product followed by a brief summary of each step and the list of the major documents of the quality system associated with each step (from the acquisition of raw material and finalize in the finished product, including all stages of approval of quality control of the company) - Description of the efficacy and safety of medical devices. In case of the description do not prove the efficacy and safety of the product, please provide a clinical research for the product.
6	Yes
7	No
8	No
9	Yes
10	*No answer provided*

Question	**RUSSIA**
1	Federal Service on Healthcare Surveillance (Roszdravnadzor)
2	Yes
3	No
4	from 50 till 110 days
5	No
6	Yes
7	No
8	Yes (Remark: CE mark is not prohibited but no any 'mutual recognition' conception.)
9	No
10	Neither EU nor US oriented

Question	**INDIA**
	No feedback received from Local Regulatory Affairs Manager.

Question	**CHINA**
1	Chinese Food and Drug Administration (CFDA)
2	Yes. There is comprehensive regulation system for medical device in China. The

	current regulation specific for medical device registration is promulgated in 2004. Reformations are ongoing, but not yet enforced.
3	Yes. 1. For class II/III medical device, CFDA authorized test lab should be involved to conduct the type test according to product specification. 2. If local trial is required, CFDA authorized study sites should be involved to conduct local study to validate the safety and efficacy of the product. 3. Medical Device evaluation center will be responsible for evaluation of the dossier, and involve advisory board if necessary.
4	Too many factors may affect the timeline, such as on dossier quality; if/not to involve advisory board...etc. Officially it will take 105 working days excluding the time for supplementary/life cycle management. In general the applications could be approved within 1 year if the product is not First in human/with high risk.
5	Yes. 1. Certificate documents: such as ISO 13485 of the legal manufacturer; approval from the source country etc. 2. Authorization/declaration letters: such as quality guarantee; self-declaration; agency appointment for registration/attorney/after sale's. 3. Technical documents: specification and QC test report at local test lab; UG and other technical documents such as IEC report; risk analysis report and technical report if necessary. 4. Clinical documents: CSR, if necessary CCSR.
6	There is no definite yes/no. Need to be assessed according to appendix 12 of the registration regulation.
7	No. However there are certain policies/methods to control the pricing and reimbursement, normally the price will be controlled through public tenders. But the policy for pricing and reimbursement may vary in different areas.
8	Yes. The China registration requires the product to be approved from the source country at first.
9	No.
10	Neither EU, nor US oriented

Question	**SOUTH AFRICA**
1	Today: Department of Health; Directorate of Radiation Control In future: South African Health Products Regulatory Authority (SAHPRA)
2	No. Being finalized for implementation by the New Combined Regulatory Body for Pharmaceuticals & Medical Devices.
3	No.
4	Listing, less than a month.
5	No.
6	No. Medical Devices which emit radiation are the only ones assessed, which is actually rather a Radiation Control Assessment than a Device Review.
7	No. Pricing regulations is applicable only to Pharmaceuticals
8	Yes. It is recommended to have it.
9	No. If available, would be submitted, but not specified
10	neither EU, nor US oriented

Question	MEXICO
1	COFEPRIS (Comision Federal para Proteccion contra Riesgos Sanitarios)
2	Yes
3	No
4	18 - 24 months
5	Yes. Manufacturing process ,Analytical certificates, Manual, Analytical method, FSC, GMPs , Specifications etc.
6	No
7	No
8	Yes
9	Yes
10	Equal to EU

Question	INDONESIA
1	Ministry of Health (KEMKES)
2	Yes.
3	No.
4	We will send by email.
5	Yes. Common Submission Dossier Template (CSDT) Format
6	No. International clinical studies are accepted.
7	No.
8	Yes.
9	Yes.
10	Similar to US.

Question	SOUTH KOREA
1	Ministry of Food and Drug Safety (MFDS)
2	Yes.
3	Yes. Assessment of technical documents for 2nd grade medical device is done by designated institutes, which are certified by MFDS. Assessment of technical documents for 3rd and 4th grade medical devices is done by MFDS.
4	1st grade medical device: about 2 weeks - 1 months 2nd grade medical device: about 4-6 months 3rd and 4th grade medical device: 6-10 months
5	Yes. STED format for 4th grade medical device will become mandatory requirement from Jan 2014. STED format for 1st- 3rd grade device can be accepted but not a mandatory requirement
6	No. MFDS recently announced draft revision of the regulation which mandates submission of clinical data for the assessment of technical documents. It is relevant for designated medical devices with higher risks. Currently intensive discussion between MFDS and the industries are ongoing, not yet finalized.
7	Yes. I'll check availability of English version of the regulation
8	No

9	No
10	neither EU, nor US oriented

Question	TURKEY
1	Ministry of Health/Turkish Drugs and Medical Devices Institution
2	There is a medical device regulation in Turkey. It is first published on 13.03.2002. There had been some revisions on it till 2011. There is not an ongoing reformation related to this regulation.
3	For the medical devices classes in IIa, IIb and III, EC certificate is a must for the registration in Turkey and these certificates should be arranged by the notified bodies. Since Bayer Turk is the importer company, we only request the EC certificates from the global contacts and we are not directly involved in the notified body processes.
4	The approval process can be described as the following and this process is valid for all device classes; Medical devices should be registered into national data bank system (TITUBB) operated by Ministry of Health in Turkey. Registration is conducted in two phases: PHASE I – DOCUMENT APPROVAL -Documents uploaded to TITUBB -Hard-copy submission of the related docs -Document approval in TITUBB PHASE II – PRODUCT APPROVAL -Product registration in TITUBB -Hard-copy notification that product registration is completed –Final product approval The whole process takes appr. 3 months.
5	No classification. As in EU regulation medical devices has three classifications which are: Class I Class II: Class IIa and Class IIb Class III For Class III, necessary documents are listed below: - (Annex 2 – Full Quality Assurance) - EC Type Examination - Annex II (4) certificate (design examination) - ISO Certificate -DoC (Declaration of conformity) -IFU (Instruction for use in Turkish) (IFU must contain revision date. According to our regulation, revision date is the date of the last text update.) For Class IIa, IIb, necessary documents are listed below: - (Annex 2 – Full Quality Assurance) -EC Type Examination - ISO Certificate -DoC (Declaration of conformity) -IFU (Instruction for use in Turkish) (IFU must contain revision date. According to our regulation, revision date is the date of the last text update.) For Class I, necessary documents are listed below: - DoC
6	No
7	No
8	Yes
9	No, Free Sales Certificate is not necessary for the registration of a medical device as RA perspective.
10	*No answer provided*

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Eidesstaatliche Erklärung

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

_____

Melanie Rosslan