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GLOBAL REGULATIONS ON THE APPROVALS, MANUFACTURER AND MARKETING OF MEDICAL DEVICES IN REGULATED COUNTRIES AND EMERGING MARKETS

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ABSTRACT

Devices are one of the most important health intervention tools available for the prevention, diagnosis and treatment of diseases, and for the patient rehabilitation. However access to these devices is an ongoing challenge particularly in low- and middle income countries (LMICs).The emergency care research institute (ECRI) nomenclature called the universal medical device nomenclature system (UMDNS) the UMDNS terms are harmonized with the classification system of the USMA and exist in ten languages. The global medical device nomenclature (GMDN) codes. The GMDN code is built according to EN ISO 15225 and is a collaborating between the EU, EFTA, USA and Canada. The GMDN terms only exit in English but can be translated with special software. This nomenclature system is required for registering a medical device within the EU. The global harmonization task force described further down has developed a recommended classification system where medical devices are divided into class A, B, C & D where class D represents the highest risk. The world health organization (WHO), with support from the European Union (EU) developed to analyze the barriers in emerging markets to increasing access to safe and high quality medical devices and to examine the contribution that local production and technology transfer of medical devices. The effectiveness of existing regulatory frameworks for medical devices in regulated countries to ensure their performance, safety, and quality. This article provides a comparative analysis of medical device regulation in the various countries jurisdictions, explores current reforms to improve the existing systems and discusses additional actions that should be considered to fully meet this aim. Medical device regulation must be improved to safe guard public health and ensure that high-quality and effective technologies reach patients. These regulatory systems differ in their mandate and orientation, organization, pre- and post-market evidence requirements, and transparency of process. Despite these differences, these jurisdictions face similar challenges for ensuring that only safe and effective devices reach the market, monitoring real world use, and exchanging pertinent information on devices with key users such as clinicians and patients. This paper examines the regulatory requirements for medical devices in Argentina, Brazil, Canada, India, Japan, Mexico and Russia, principally focused on strengthening regulatory processes, enhancing post market regulation through more robust surveillance systems and improving the traceability and monitoring of devices. Some changes in premarket requirements for devices are being considered.

Keywords: LMICS, ECRI, WHO, Premarket requirements, Medical devices.

INTRODUCTION

Health technologies (e.g. medicines, vaccines and medical devices) are an indispensable component of effective health care systems. Among these technologies, medical devices provide the foundation for prevention, diagnosis, treatment of illness and disease and rehabilitation. There are over 10000 types of medical devices, ranging from basic tongue depressors, stethoscopes, surgical instruments, prostheses, and in - vitro diagnostics, to complex medical diagnostic imaging equipment. The availability, accessibility and effective use of essential medical devices play an important role in the achievement of health system

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performance goals and the cost and quality of medical care that a population receives.

Medical devices are becoming more important in the health care sector. Today there are more than 8000 generic medical device groups where some devices contain drugs [1]. This increases the demand for better regulatory frameworks to ensure that products entering the market are safe and efficient. One of the major issues for companies developing and producing medical devices is to be updated on the regulatory requirements and implement them in the process. A company that does not succeed with this may loose thousands of dollars in the delay of marketing the product [2].

A medical device is according to the European definition "any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- Diagnosis, prevention, monitoring, treatment or alleviation of disease,
- Diagnosis, monitoring, treatment, alleviation of or compensation for an injury orhandicap,
- Investigation, replacement or modification of the anatomy or of a physiological process,
- Control of conception and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means [3].

Classification of medical devices

Classification of medical devices is necessary to apply correct regulations and quality systems.
The classification levels are:

In the United States medical devices are classified as class I (General Controls), II (Special Controls) or III (Pre-market Approval) devices where class III devices represent the highest risk and require more control. Medical devices are classified through a classification database found at the FDA homepage and are given a seven digit number based on the product category [4].

In the European Union general medical devices are classified as class I, class Isterile, class I measuring, class IIa, class IIb or class III where class III devices represent the highest risk. Active implantable medical devices are not classified and in vitro diagnostic devices have their own classification system. Information on the European classification system is found in MEDDEV 2.4/1. The classification rules are found in Annex IX of Directive 93/42/EEG. See table 1[5].

In-vitro diagnostic medical devices (IVDS) are regulated as a subset of medical devices, and separately categorized in class 1 to 4 [6], with similar risk levels to medical devices, and based on the same GHTF recommendations [7]. A nomenclature is usually given to a medical device when it is classified. There are two international nomenclatures that are very common:

The Emergency Care Research Institute (ECRI) nomenclature called the Universal Medical Device Nomenclature System (UMDNS). The UMDNS terms are harmonized with the classification system of the USA and exist in ten languages [8].

The Global Medical Device Nomenclature (GMDN) codes. The GMND code is built according to EN ISO 15225 and is collaboration between the EU, EFTA, USA and Canada [9]. The GMDN terms only exist in English but can be translated with special software. This nomenclature system is required for registering a medical device within the E.U [10]. Both systems consist of defined terms that describe a group of products with similar characteristics. The GMDN system is developed from 6 different nomenclature systems and the UMDNS system is one of them. GMDN and UMDNS harmonize with each other but GMDN has more terms and is thereforePreferred [11].

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 [12].

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 and is covered by 21 CFR, Part 814, Subpart B [13]. 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.

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 [14].

Submission Requirements to medical devices

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) [15].

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 [16].

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 [17].

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 2, the 'Proposed Regulation' offers some alternatives to the manufacturer to undertake the conformity assessment procedure for medical devices.

Declaration of Conformity

Once a medical device has undergone an assessment and complies with the requirements of the applicable regulation, a CE marking (Figure 1) shall be affixed to the product according to Article 18 of the 'Proposed Regulation'. 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 [18, 19].

Objective of the work

- Analyse the current research in technology transfer and local production of medical devices in countries.
- Understand barriers and challenges to access of medical devices particularly in various countries.
- Develop proposals to overcome barriers across the world to improve access to medical devices and
- Comprehend and analyses feasibility to produce medical devices within LICs content as a way to improve access to them.

METHODOLOGY

Comprehensive literature review

It is carried out to understand the context of what has been defined as access to medical devices, namely the current situation of the medical device industry and market, related processes and elements in the development of medical devices such as research and innovation of medical technologies and aspects related to financing and regulation of medical devices.an analysis of past research carried out by WHO on medical devices was also performed.

To explain the current global situation of the medical device market and local production, data were firstly obtained by reviewing the existing medical devices literature. This included peer-reviewed journal articles and grey literature, as well as reports published by public international agencies and private non-governmental organizations (NGOS) all these sources provided a first approach to gathering for the scoping study. Although information on the topic is limited effort was made to identify country-specific studies (specifically for five countries from the various WHO regions) on the local production and development of medical devices. Analysis was performed on the current global market for medical devices, research and development capacity, health systems

financing, partnerships and collaborations to support development of technologies, governance and regulations.

Barriers to production of medical devices were identified in the literature and compared to actual barriers found on the field by surviving a group of stakeholders. A survey was designed based on the findings of existing WHO publications on access to medical devices.

Based on the findings from literature review and the survey, a first draft of a feasibility tool to measure the possibility for a device to be produced and a successfully commercialized in a LIMCs was developed.

The efficiency of feasibility tool was tested on various projects and the results were analysed. Other, similar tools were then sought and recommendation for future improvements were complied.

Finally, a stakeholder group consultation was organized to discuss the draft report and the feasibility tool successful case studies were also considered as examples of improving access to medical devices and eliminating barriers to their local production in LIMCs.

MEDICAL DEVICE APPROVAL PROCESS IN REGULATED AND EMERGING COUNTRIES

Argentina

Regulation

Medical devices are regulated by the National administration of drugs, food stuffs and medical technology (ANMAT) under the ministry of health. Medical products in Argentina and importers of medical devices must be registered with ANMAT. The importer is responsible for registration of medical devices [20].

Device registration

The manufacturer or importer must register all reclamations and send a copy of the form to sistema national de techno vigilancia at ANMAT. Signed by an authorized person, declaring the number on the reclamation. The technical documentation required for product registration. Manufacturer and importers of medical devices class 2,3& 4 need to provide following information together with the application:

A declaration of payment of the corresponding product registering fee.

Information for identification of manufacturer and importer of medical devices and the product description.

A copy of the manufacturer allowance to commercialize its medical device and description of the manufacturer, exporter and the importer.

A certificate of company authorization can only be given to a company that already have a GMP certificate.

For imported medical devices a certificate of fee sale equivalent documentation from a competent authority is required from where the medical device is produced or commercialized.

A declaration of conformity with the MERCOSUR legislation. Manufacturer and importers of medical devices class 1 need to provide the information in the 1st two points and the last point. Operation manuals, instructions for use, labels and the catalogs shall be submitted with the application [21].

Brazil

Regulation

The national health survivallence agency (ANIVASA) or in Portuguese agency national de vigilenciasanitaria (ANIVASA) is the competent authority for medical devices in Brazil. All medical devices, diagnostic kits, immune biological products and sanitation products must be registered with the ANIVASA before getting out on the Brazilian market [22].

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, see table 3.

Device registration

The required documentation for the registration of a medical devices is :

A copy of payment bank receipt provided by the ANIVASA a declaration of company fee shall also be submitted with the application.

Identification of the manufacture or importer and its medical device declaring the technical and legal responsible.

A copy of authorization of the manufacture to import and commercialize its medical devices in the country, when authorized to importer or export the commercial relationship between the manufacturer.

A copy of registration or certificate fee trade or equivalent document issued by the competent authority where the product is manufactured and or commercialized [23].

Canada

Regulation

Under the authority of food and drug act,regulates the sale of drugs and medical devices in Canada. Health Canada is divided into two parts:

Health products and food, and therapeutic products directorate. Medical devices bureau is under therapeutic product directorate which is divided in to device evaluation,licencing services and research and survivallence [24].

Device registration

There are licenses for single devices,medical devices family,medical device group,medical device group family, system and test kit information required in the application for a new medical device license is [25]

- Device classification
- Device name
- Application history

- Name and address of the manufacturer as it appears on the device label
- Mailing address for regulatory correspondence
- License application type
- Device preferred name code
- If the device is a near patient IVDD
- If the IVDD is sold for home use
- Device usage category
- If the device containing a drug
- Purpose of the device
- Device details
- List of standards complied with in the manufacturer of the device
- Attestation of safety and effectiveness
- Attestation of labeling
- Attestation of investigational testing for IVDD
- Evidence of safety and effectiveness
- Attestation of drug safety and efficacy and quality
- Information on each part above and what differs between the classes is found in the guidance on the complete the application for a new medical device.
- License and preparation of a premarket review document foe class 3 and class 4 device license application other information is found in the regulations [26].

India

Regulations

The development of health under India's Ministry of health and family welfare is responsible for the jurisdictions over the regulation of medical devices. The central drug standard control organizations (CDSCO) in the ministry of health is primarily responsible for regulations of drugs but also medical devices, diagnostic devices and cosmetics [27].

Device registration

The drug controller general of India (DCGIs) wants applicant details such as name, address and contact number of the applicant the master file shall have a description of components and materials used and information on the manufacturing process including flow charts, quality assurance procedures and process controls, risk management according to ISO 14971 and test protocols and reports for stability, biocompatibility, toxicology and validation/verification of sterilization where these tests are applicable [28].

Labeling of devices according to GHTF guidelines or ISO specifications is accepted. Manufacturers of medical devices shall have documented procedures for distribution records, complaint handling, adverse incident reporting and product recall. A registration of medical devices defined as drug is valid for 5 years [29].

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) [30]

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 [31].

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 Licensee in Form-28 for manufacture of Medical Devices'[32]. 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 [33].

Japan

Regulations

The ministry of health, labour and welfare (WHLW) is responsible for food, medical care, labour policy, and labour standards and social welfare. The pharmaceutical and food bureau within the ministry is responsible for pharmaceutical and medical device regulatory policy making [34].

Device registration

The certifications are done by the third party certification bodies. These certification bodies have to be Japanese and cannot be a European notified body. Examples of third party notifications bodies are TUV, SUD, BSI japan and Japanese standards association. The MAH is responsible for risk management. ISO 14971 has been adopted by the japan but it is not mandatory [35]. A medical device manufacture in japan needs to obtain two licenses.one is the license given to a MAH and one is the license for manufacture. Foreign medical device manufacture do not needed a MAH license themselves, or a license for manufacture, but need to register their company.

Comparison of Content of submission in above countries

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. 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. 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. Figure 2 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, see figure 2.

Comparison of Timing of submission in above countries

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. 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. Figure 3 presents a potential submission and approval plan. Looking at EU and Brazil, this implies that from submission to approval in the EU it would take nine months see figure 3. 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.
(According to Country Questionnaire, 2014 and Emergogroup) illustrates which countries need a FSC for submission and which countries do not require a FSC.

Global marketing of medical devices

Emerging markets will even be responsible to balance the downward trend in some of the developed markets over the next years. Considering this outlook, it is important to understand these markets with regard to their local legislations for medical devices Representative groups for emerging countries are BRICS and MIST. 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 [36-38]. 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.

Global Competitiveness

The U.S. is the largest consumer of medical devices and leads the world in the production of medical devices. The U.S. has a medical device market valued at more than $100 billion in 2008, roughly 42 percent of the world's total. U.S. exports of medical devices in the key product categories identified in Section I (excluding IVDs) was valued at approximately $31.4 billion in2008 and imports were valued at $33.6 billion. The surgical and medical instruments category comprises the largest trade category within the medical device sector. This category includes numerous price-sensitive lowertechnology devices where imports can be more easily substituted than with higher technology medical device products. While exports of surgical and medical instruments grew 61.54 percent from 2002 to 2007, imports more than doubled over the same period.

Impact of middle-class growth of medical device marketing in BRIC

China and India are nations where the majority of the population falls under the lower income range of less than $3000 per annum, but these countries are characterized by high savings. The number of people with incomes above $3,000 per annum – the middle-class – has been steadily increasing over the past five to 10 years.The rising middle-class creates a demand potential in all forms of enhanced lifestyle, including healthcare. The share of medical device exports to the BRIC nations is increasing from both developed and emerging countries, and this trend is likely to continue as demand from BRIC consumers rises in the next decade.

Emerging markets overview

Classification of emerging markets

IMS Health classifies emerging nations in the pharmaceutical sector into three tiers under its "Pharma emerging Markets" description. However, there is so similar classification of emerging markets with respect to medicaldevices. Business Insights has made the first attempt to categorize prominent emerging nations under different tiers with this report.

Tier 1 – **China**: China is only country to be included in the top tier. Among emerging nations, it is the country with the largest medical device market size and has double-digit growth rates. Moreover, evolution of medical device regulation is fastest in China and over the forecast

period up to 2015 it will emerge as a global medical device manufacturing hub with production protocols comparable to developed nations. Business Insights estimates that China will be a stand-alone country in the top tier of emerging medical device markets until 2015.

Tier 2 – **India and Brazil**: While the medical device market sizes of India and Brazil are not as large as China's, Brazil and India are among the fastest growing medical devices markets. The reason they are classified under Tier 2 is not only because of their smaller market size in comparison to China, but also because of their evolving regulations. In India, new medical device regulations are expected to take effect from 2011 and Brazil has started to impose good manufacturing practices (GMP) protocols only since 2009 on its medical device manufacturing sector. Given the strong technical backgrounds available in these countries, they have the potential to become Tier 1 countries after 2015.

Tier 3 – **Other emerging nations**: These include Russia, Turkey, Vietnam, Argentina, Chile, South Korea, Malaysia, and Mexico. While Mexico and Russia are the largest markets for medical devices in this tier, they are limited by the fact that, despite strong technical backgrounds, they have ineffective manufacturing protocols to develop indigenous medical device manufacturing. Given their growth rates, Mexico and Russia could become Tier 2 countries after 2015, but never in the league of Tier 1. Other nations would continue to remain in Tier 3 owing to their small market size for medical devices.

The emerging economies of Brazil, Russia, India & china (BRIC) have become lucrative, high growth markets for medical devices. The device market in developed nations such as the US, Europe and japan has reached saturation and the economic recession has restricted growth in these countries over the past two years.

The growing middle-class in the BRIC nations has reached more than the one billion in population and this trend implies a surge in value-added lifestyle. The combined gross domestic product (GDP) of BRIC was about 31% of the global economy in 2009 owing to their increased share in global outsourcing and offshoring.

BRIC versus global competition on medical devices marketing:

The US is the largest consumer of medical devices and leads the world in their production. Its medical device market was valued at $96.7bn in 2009, about 43% of the World's total. Exports from the US alone accounted for over $33bn in 2009.medical device imports from developed nations such as US, Germany, France, and Japan have been consistently increasing in the BRIC countries.

Figure 4 represents the global medical imaging revenues in 2009 and reflects the sales of medical imaging equipment such as MRI, CT, and ultrasound. While the US and Europe are dominant with more than 70% of the global total, the emerging nations contributed to about 14% of the total revenues in 2009. Imaging equipment encompasses high-end products that are mostly imported by the emerging nations from the US, Europe, and Japan.

Figure 5 represents the global medical device market size (not including medical imaging equipment). These revenues reflect only the medical products pertaining to cardiovascular, orthopedics, surgical devices, ophthalmic, wound care, neurology, urology, gynecology, respiratory, and endoscopy segments. The US and Europe comprised over 77% of the total revenues in the devices industry in 2009,while the emerging nations contributed to only 9.3%.The global medical device market size is disclosed below in figure 4 and 5.

Comparision of market environment for medical devices in some countries

China medical device marketing:

The Chinese medical device market under went fast-paced growth in last five years in comparison to developed markets such as the US, United Kingdom, Japan and Germany. A major factor contributing to growth is that demand is outpacing the supply by approximately 40%. Others drivers include increase in the patient population and increased govt. healthcare expenditure. See figure 6

India marketing

The medical device market in India is expected to reach $3.2bn in 2010. A growth of 13.4% over 2009 and as high as 20% by the end of 2015. About 50% of the medical devices revenues ($1.4bn) in 2009 were contributed by imported products that include high end scanners in June 2009, the drug consultative committee (DCC) and the drug technical advisory board (DTAB) approved new formal regulations for India's medical device sector. The health ministry is set to issue the notification of the new regulations in the near future. See figure 7

Brazil marketing

Brazil is the only Latin American country classified in the top four emerging nations for medical devices. It has the largest medical devices market in Latin America followed by Mexico and Argentina. The Brazilian medical device market was valued at $3.2bn in 2009, a 10% increase over the previous year. Over 35-40% of the medical devices imported into Brazil come from the US. And unlike India and china the country has a well-established network of distributors, wholesalers and retailers who import medical equipment from all over the world, see figure 8.

Russian marketing

The Russian govt. is to renovate about 80% of Russian medical institutions from 2011-2012. One third of these facilities are considered to be unusable. This is an extension of an earlier govt. announcement that 30% of its healthcare facilities are to be repaired by April 2010.An

increase of 2% in medical device spending as proportion of total health care spending from 2009-2010 makes Russia an attractive investment destination for multinationals, see figure 9

Global medical devices market

It is important to identify the obstacles for commercializing and selling medical devices in low-resource settings. On barriers to the development of medical device, figure 10 shows existing obstacles for the commercialization of products or for entering the market. The most important barriers mentioned by respondents were: financing, regulatory clearance and production and manufacturing issues.

As shown in figure 11, the 2005–2009 medical device patent applications were dominated by OECD countries, with 42% of patents filed in the United States alone. China's share (4.1%) deserves special mention. It is roughly half the size of Germany's, and patent applications are increasing. The Chinese approach to patenting is discussed in further detail in the Country case studies section.

A growing number of multinational companies (MNCs) are setting up manufacturing sites and research centers in LMICs, particularly in emerging BRIC markets (e.g. Brazil, Russian Federation, India and China) that are becoming powerhouses in producing generic drugs and low-cost healthtechnologies. LMICs boosted their share of R&D expenditure by 13% between 1993 and 2009 [39]. However, significantly, LICs without an innovation climate are often spectators in this field and it is common to find a dependence on so-called "off-the-shelf" imported technology.

Among all 67 countries surveyed by The World Medical Markets Fact Book, LMICs account for nearly 13% of the global medical devices market. In this category, the top five manufacturers – Brazil, China, India, Mexico and the Russian Federation – produce 64% of market needs in LMICs [40]. Furthermore, while Asia, Europe, and Latin America are well represented, Africa is conspicuously under-represented in manufacturing capacity. Africa has a wide range of health contexts ranging from 1100 maternal deaths per 100 000 live births to Tunisia's 56. This demands meaningful, customized approaches to medical device production, procurement and delivery that are sensitive to local contexts. See table 4.

Local production may be a viable, cost-effective means to improve access to simple medical devices. However, in instances where local production is insufficient or uneconomical, imports, aid interventions and/or foreign direct investment can help address needs. Table 8 lists the top ten African countries in medical device import and export sales. A large proportion of medical devices are imported from outside of Africa. The leading suppliers of medicaldevices (by revenue) to the African region are: Germany, France, the UnitedStates, China, and the United Kingdom.

Table 1. Classification of medical devices with level of risk

Classification	Level of risk
Class 1(non-measuring/non sterile)	Low
Class 1-supplied sterile Class 1-incorporating a measuring function Class 2a	Low-medium
Class 2b	Medium-high
Class 3 including active implantable medical devices(AIMD)	High risk

Table 2. Conformity assessment procedures in the European Union (According to European Commission and Emergo group

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

Table 3. Review timelines with some exceptions depending on category and class

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

Table 4. Top ten countries by medical device sales revenue

Country	Sales Revenue (US$ millions)	Percentage (%)
United States of America	100 801	39.0
Japan	29 208	11.3
Germany	19 596	7.6
France	8890	3.4
United Kingdom	8477	3.3
Italy	8360	3.2
China	7811	3.0
Canada	5779	2.2
Russian Federation	5186	2.0
Spain	4602	1.8
Subtotal	198 710	76.9
Total (67 countries)	258 424	100

Table 5. Top ten African countries by value of medical device imports andexports

Country	Imports (US$ millions)	Country	Exports (US$ millions)
South Africa	670.1	South Africa	111.5
Egypt	405.5	Tunisia	98.8
Algeria	307.7	Egypt	40.0
Morocco	171.1	Morocco	14.7
Tunisia	145.4	Mauritius	8.1
Libyan Arab Jamahiriya	141.1	Kenya	4.1
Nigeria	119.4	Swaziland	1.7
Angola	87.8	Madagascar	1.3
Sudan	56.2	Sierra Leone	0.9
Kenya	50.2	Libyan Arab Jamahiriya	0.9

Fig 1. CE marking

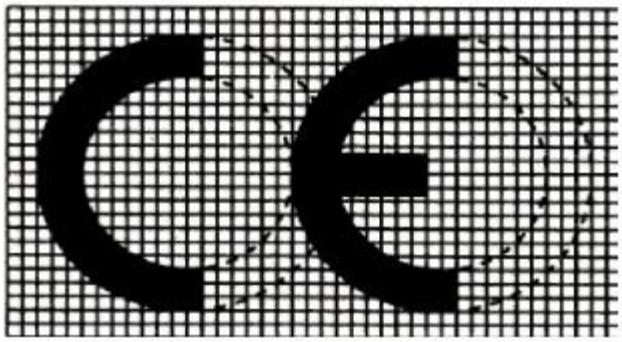


Fig 2. Need for Free Sales Certificates

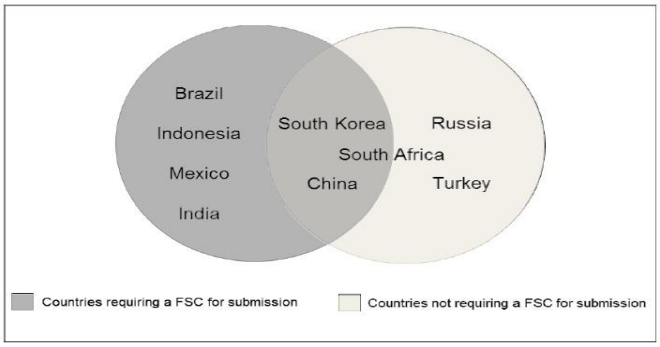


Fig 3. Illustrates these countries can start with their submissions whenever the documentation has been compiled for submission by the manufacturer

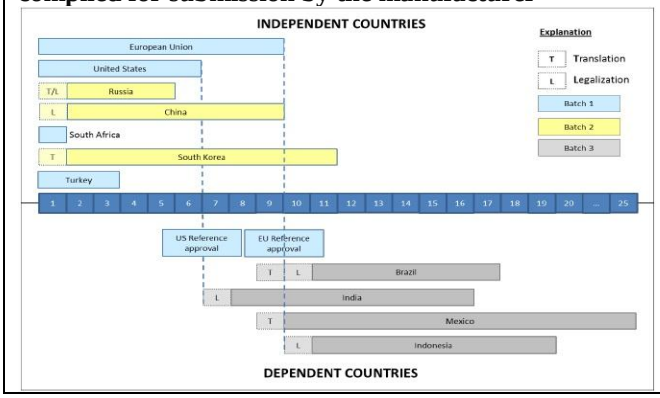


Fig 4. Medical imaging global market size 2009

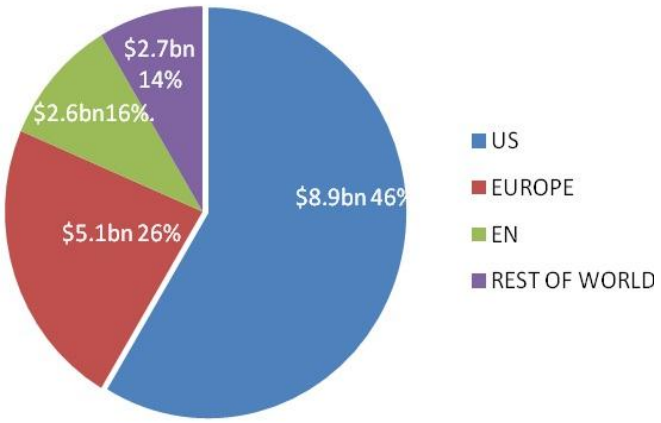


Fig 5. Medical devices-global size 2009

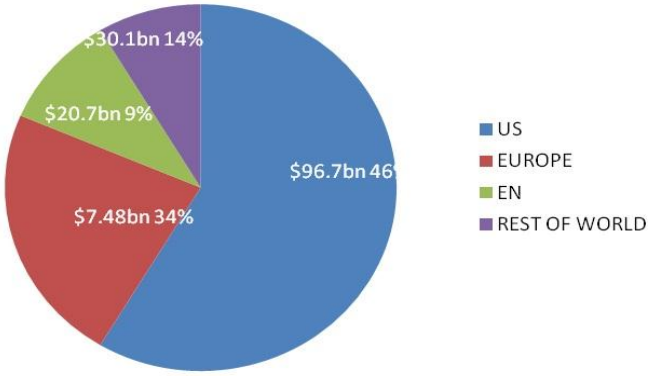


Fig 6. China medical device market size and growth forecast 2009-2015

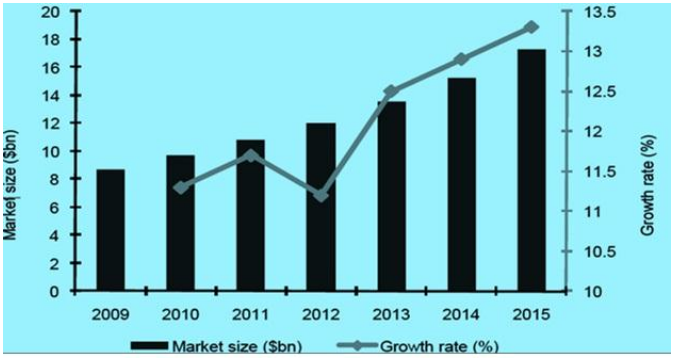


Fig 7. India medical device market size and growth forecast 2009-2015

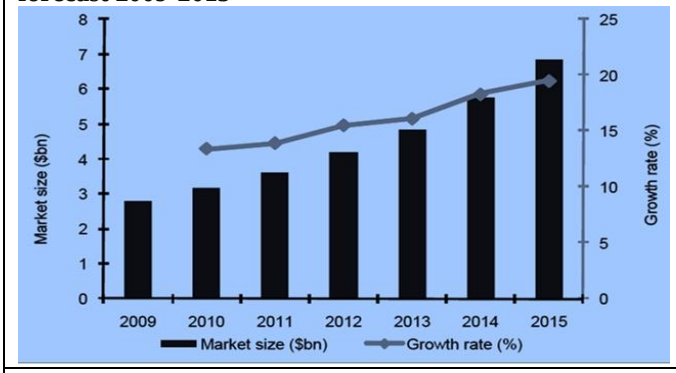


Fig 8. Brazil medical device market size and growth forecast 2009-2010

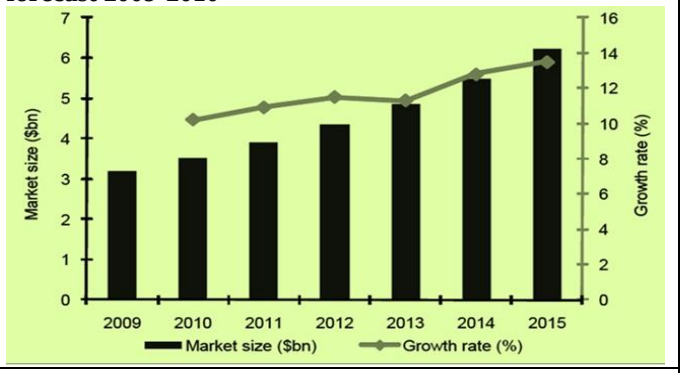


Fig 9. Russia medical device market size and growth forecast 2009-2015

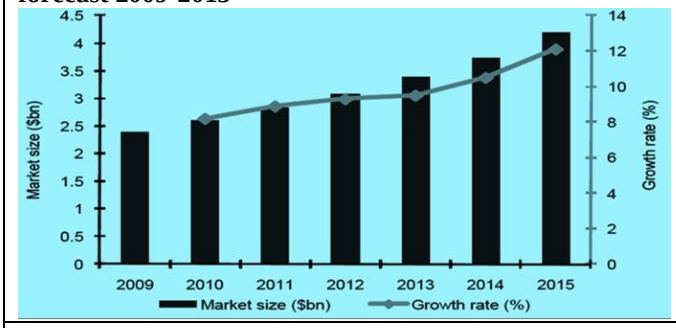


Fig 10. Barriers faced in commercializing/selling medical devices

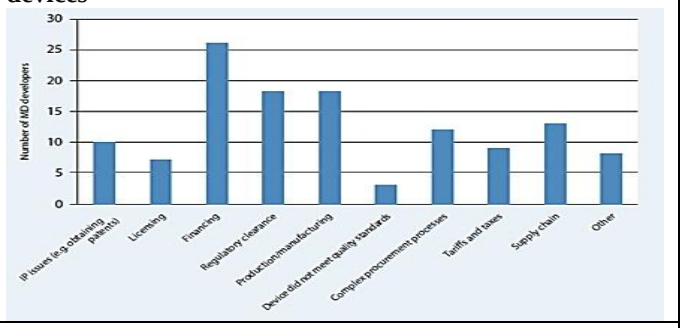
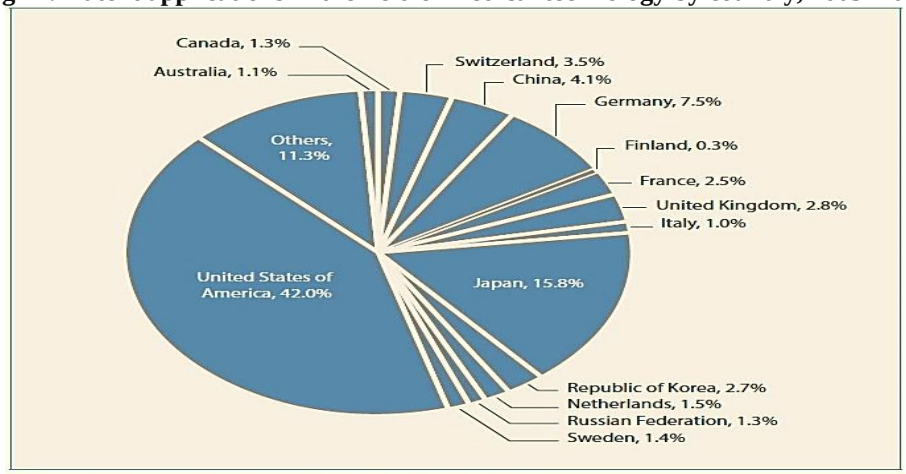


Fig 11. Patent applications in the field of medical technology by country, 2005–2009



CONCLUSION

Most countries have similar requirements for registration of medical devices and are striving to harmonize with the GHTF guidelines. Classification of medical devices is usually done in accordance with the EU system, FDA system; 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. 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. GHTF guidelines or by catalogue. The nomenclature is UMDNS codes or GMDN where GMDN seems to be the most common variant. Main requirements are a local representative, a Certificate of Free Sale from the country of origin, import license from the competent authority in the import country and registration of the company and the product. Quality management systems and risk management systems are in most countries required, except for medical devices class I. Certificates of ISO 13485 and ISO 14971 are required or recommended. The current reforms address some of the outstanding challenges in device regulation, additional steps are needed to improve existing policy. We examine a number of actions to be considered, such as requiring high-quality evidence of benefit for medium- and high-risk devices; moving toward greater centralization and coordination of regulatory approval in Europe; creating links between device identifier systems and existing data collection tools, such as electronic health records; and fostering increased and more effective use of registries to ensure safe post market use of new and existing devices.

REFERENCES

1. World Health Organization. Sixtieth World Health Assembly, ProvisionalAgenda, 2007.
2. Peter L. Medicintekniskaprodukter – Vägledning till CE märking, SIS Förlag AB, Stockholm, 2007.
3. European Commission. Directive 93/42/EEC, at http://eur-lex.europa.eu, 2008.
4. U.S. Food and Drug Administration. Overview of Device Regulations at www.fda.gov/cdrh/devadvice/overview.html, 2007.
5. Review of medicines and medical device regulations. Ibid, 74, 2014.
6. Therapeutic Goods Administration. Overview of the regulatory framework for in-vitro diagnostic medical devices, 2011b.
7. Review of medicines and medical device regulations. Ibid, 2014.
8. ECRI Institute. Universal Medical Device Nomenclature System, 2008.
9. http://www.mercosur.int/msweb/portal%20intermediario/es/index.htm,
10. Medical Products Agency. Global Medical Device Nomenclature, http://www.lakemedelsverket.se/Tpl, 2006.
11. U.S Food and Drug Administration. Brockton Hefflin and Larry Kessler ,The Global Medical Device Nomenclature, 2008.
12. US FDA. "Premarket Notification (510k)." <http://www.fda.gov/Medical Devices/Device Regulation and Guidance/HowtoMarketYourDevice/ Premarket Submissions/ PremarketNotification510k/default, 2014.
13. US FDA. "Premarket Approval (PMA)." "<http://www.fda.gov/ MedicalDevices/ DeviceRegulationandGuidance, 2013.
14. USFDA. "Special Considerations."<http://www.fda.gov/ MedicalDevices /DeviceRegulationandGuidance/HowtoMarket YourDevice/PremarketSubmissions/PremarketNotification510k/ucm134578, 2014.
15. US FDA (United States Food and Drug Administration). Classify Your Medical Device."<http://www.fda.gov/ MedicalDevices/DeviceRegulationandGuidance/Overview/ClassifyYourDevice/default, 2014.
16. Thomson Reuters. Regulatory Summary. How to market medical devices (United States). *IDRAC*, 48, 186, 2013.

17. US FDA (United States Food and Drug Administration). Summary Technical Document (STED, PilotProgram."<http://www.fda.gov/ MedicalDevices/ Device Regulationand Guidance/ HowtoMarket YourDevice/ Premarket Submissions/Summary Technical DocumentSTEDPilot, 2014.
18. TÜV SÜD Product Service GmbH. Guidance Technical Files and Design Dossiers for Non Active Medical Devices." <http://www.tuev-sued.de/uploads/images/1384776326212587860065/guidance-design-dossiers.pdf, 2014.
19. European Commission. CE marking makes Europe yours. <http://ec.europa.eu/enterprise/policies/single-market goods/ce marking/downloads/ ce_brochure_en.pdf, 2013.
20. International Trade Administration. Medical Device Regulatory Requirements for Argentina, 2006.
21. ANMAT. gustin M. Iglesias Diez,Registro de Productos Medicos, Demostracion de Seguridad y Eficacia, 2007.
22. ANVISA. http://www.anvisa.gov.br/eng/index.htm, 2008.
23. ANVISA. Resolucíao RDC, 2001.
24. Canadian Medical Devices Industry. Medical Device Regulatory Framework, created, 2007.
25. Department of Justice Canada. Medical Devices Regulations, 2007.
26. Health Canada. Health Products and Food Branch Inspectorate, Guidance on Medical Device Establishment Licensing, 2007.
27. International Trade Administration. Medical Device Regulatory Requirements for India, 2005.
28. Central Drugs Standard Control Organization. Clarification on Guidelines for Import and Manufacture of Medical Devices, 2008.
29. Central Drugs Standard Control Organization. Drugs and Cosmetic Act 1940, 2005.
30. CDSCO. Guidance Document on Common Submission Format for Registration/ Re-Registration of Notified Medical Devices in India, 2012.
31. CDSCO. Guidance Document on Common Submission Format for Import License in Form-10 of Notified Medical Devices in India, 2012.
32. CDSCO. Guidance document on application for grant of Licensee in Form-28 for manufacture of Medical Devices in India under CLAA Scheme", Document No. CDSCO/MD/GD/CLAA/01/00.
33. Pacific Bridge Medical. The New Market Authorization Holder (MAH) System for Medical Devices in Japan, 2007.
34. TUVSUD. The Regulatory System and Requirements in Japan for Medical Devices, The New Pharmaceutical Affairs Law, 2006.
35. Pharmaceuticals and Medical Devices Agency. The Revised Japanese Legislation for Medical Devices, 2006.
36. Emergogroup. Obtaining a Certificate of Free Sale (CFS) for Medical Devices, 2014.
37. Emergogroup. The-Medical-Device-Regulatory-Approval Process, 2014.
38. Central Intelligence Agency. The World Factbook. Appendix B: International Organizations and Groups, 2013.
39. The world medical markets fact book. Chichester, Espicom Business Intelligence, 2011.
40. Maternal mortality ratio. Geneva, World Health Organization, 2010.