Analysis of regulatory requirements of medical devices and in-vitro diagnostics worldwide for the development of an efficient procedure of registration for manufacturers of medical products

Abstract: Due to globalization and the quick development of technology, each government aims to ensure the safety and performance of products brought to their markets to protect its population. The peoples’ health state is of great significance and influenced easily by the quality of medical products. Therefore governments enact laws, directives and regulations to assure that quality. Nevertheless, these regulations can impede innovation and create trade barriers which result in an adverse effect on national economies. Where in some states no regulatory system is installed, others have highly sophisticated registration requirements that must be met. These diversities result in a challenge especially for small and medium sized companies, whose resources are often limited. [1]

Manufacturers must control these diverse regulatory requirements by analyzing each market. Therefore an efficient procedure of registration should be defined that streamlines different registration requirements and ensures regulatory compliance. Next to regulatory authorities describing these requirements also harmonization groups play an important role in the design of the global regulatory landscape. Therefore also the most important harmonization groups and their current activities were investigated.

The analysis showed that the impact of harmonization groups can be identified easily since new defined or updated regulatory requirements are oriented on their guideline. Still the harmonization of regulatory requirements in the medical device sector is not sufficiently enhanced. Thus the confrontation with each national regulatory system is inevitable.

Keywords: Registration, medical product, harmonization, global market placement, procedure

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1 Background

At some point of the design and development phase addressing product registration is necessary for manufacturers. Already during the concept phase or latest during product development this conformity with regulatory requirements is necessary, with that a placement on the market is not delayed resulting in a financial damage for the company. [2]

The most important task is investigating different national regulatory requirements and evaluating if market placement is possible. The investigation is challenged though since information sources are often only available in national language or simply not to be found. Additionally if global market placement should be achieved, the diversity of the regulatory requirements complicates product registration.

This is where harmonization groups have taken up the task to equalize these diversities and to define consistent registration requirements. By describing one set of documents, which provides evidence for the safety and effectiveness of the product, global market placement should be possible. To achieve this goal these groups describe guidelines for governments as well as manufacturers. By analysing these guidelines, the impact on regulatory systems can be detected.

Some countries have already managed the harmonization of the regulatory requirements, for instance the member states of the European Union or the member states of the Association of Southeast Asian Nations (ASEAN). Here, each country has agreed on a regulatory framework describing requirements for the market placement of medical products. But even those countries have national variations that must be considered preparing the technical dossier.
For the market placement of medical products, it is essential for the manufacturer to identify each national regulatory requirement and to design a proper strategy for the market placement. This can only be achieved with a proper analysis of regulatory systems as well as harmonization activities. An efficient procedure of registration, which reacts on local requirements and displays them clearly, is inevitable to save valuable resources.

2 Regulatory requirements worldwide

There is a chasm between developing countries, which have hardly defined regulations for medical products yet, and the industrial states, which prescribe demanding regulations for placing such products on their markets. It is the manufacturers task to analyze the different requirements and assure their fulfillment. Weak regulation of medical products represents a major risk for the population. By prescribing them, states perceive their protecting duty for its people, but at the same time increases the costs for complying with these regulations for manufacturers, which often pass on their costs to patients. Clear regulatory requirements for protection, including the possibility of their realistic implementation for manufacturers, should be the goal of each national legislation. [1]

The most common way to achieve an efficient regulatory system is the definition of a risk-based approach of regulatory controls, in other words, a classification system. A band aid does not need the same regulatory controls as a hip prosthesis. Thus, regulatory controls are contingent upon the level of risk associated with a medical product, where risk is a combination of the probability of occurrence of any harm and severity of that harm. The result is a benefit for regulatory authorities, manufacturers, users and patients, by focusing resources on high risk products, where a close control is indispensable. Additionally, the reduction of effort for low risk products removes market barriers, enables high quality products for patients and leaves space for innovation. [2, 3]

There are two classification options for the assignment of products to the corresponding risk classes: either rule-based, or group-based. A rule-based classification system defines specific rules, which must be applied to identify the final risk classification. A group-based system defines product groups which are already assigned to a risk class. By the assignment to a product group the risk class can be determined. Another distinction can be made between a three and four-tire based system, where a trending to four-tire based systems can be derived.

2.1 Africa

In Africa there is a wide range of different and complex economic states, political instabilities and social situations that must be considered. Predominantly, the regulation of medical devices (MDs) and in-vitro devices (IVDs) in Africa is weakly defined. The access to medical products is limited due to their availability and costs. Additionally, trained personnel or laboratory facilities for the correct handling of some diagnostic tests are often missing. If a medical product is regulated or not, depends on its intended purpose. If the product lies within the scope of curing, identifying or assisting the treatment of a specific infectious disease, such as tuberculosis, malaria or HIV/AIDS, the activities toward creating or strengthening regulations are reinforced by the national regulatory authorities due to the support of help organizations. [4]

2.2 North- and South America

In North and South America, the regulatory landscape is diverse. In Northern America the Food and Drugs Administration (FDA) as well as Health Canada, which are the regulatory authorities there, rule the market of medical products. The U.S.’FDA defines three different procedures that can lead to market clearance in the United States of America dependent on the product group and a substantial equivalent product. [5]

Health Canada has recently changed their requirements for manufacturer to give prove to their Quality Management System (QMS). In January 1st of 2019 the transition deadline for the Medical Device Single Audit Program (MDSAP) passed. This means that from now on, only MDSAP certifications for manufacturer’s QMS are valid for product registration. [6]

The South American Nations have also established strict regulatory systems. Here often a registration holder, who is responsible for the communication with the regulatory authority and the registration is needed. Also, an evidence of a QMS is advised for launching in such markets. [5]

2.3 Asia

In Asia big markets like China, Japan and Russia define strict regulations that must be complied with for national market placement. Here, the language differences often complicate the procedure.

Smaller markets in South East Asia, which are members of the Association of South East Asian Nations (ASEAN) have agreed on a medical device directive (AMDD), which consists
of 24 articles, which describe inter alia, Essential Principles, Classification rules of medical devices and IVDs, conformity assessment procedures, and labeling requirements. The process of implementing the directive in each national law is though not completed yet. [7, 8]

2.4 Europe

The member states of the EU managed a harmonization of regulations for depleting trade barriers within their territory. Three directives have ruled the regulatory landscape since the 1990’s. The scopes of these directives are medical devices (93/42/EEC - MDD), active implantable medical devices (90/385/EEC - AIMD) and in-vitro diagnostic medical devices (98/79/EC - IVDD). For active implantable medical devices and medical devices complementary directives were published in 2007 to complete their regulatory requirements. [5]

These directives will be definitely replaced in 2020 by the regulation for medical devices (2017/745-MDR) and in 2022 by the regulation for in-vitro diagnostic medical devices (2017/745-IVDR), which became effective on May 25th 2017.

Generally speaking, the difference between a directive and a regulation is, that a directive must be transformed into national law by each member state of the EU, where a regulation is binding in its full extent. [9]

Content-related the most obvious change is, that there are only two regulations left. This can be explained by the scope of the MDR, which now also includes active implantable medical devices. Next to the changes of the classification systems, there are updates regarding economic operators, the creation of an EU database called EUDAMED, an obligatory Unique Device Identification (UDI), new requirements for notified bodies, stricter requirements for clinical studies, performance evaluations and post-market surveillance systems and more precise requirements for risk- and quality management and the technical documentation. Also, in comparison to the directives, the assessment of a full QMS is demanded already for products which inherited lower risk.

The new set of regulations EU was a necessary reactive measure to scandals associated with medical products. The directives left statutory gaps for faceless manufacturers to place products on the European market. Nonetheless, one major fear regarding the new regulations is a disadvantage for small companies and innovation leading to the deceleration of medical progress, which has negative impacts on the patients after all. Not only manufacturers are faced with challenges but also notified bodies, which play an important role in the conformity assessment procedures. There is a lack of specialists that perform as auditors of notified bodies, but more medical products will need their approval since many products will result in a higher risk class according to the regulation.

The total impact on the medical device sector in Europe remains to be seen, since manufacturers, notified bodies and regulatory authorities are confronted with open questions and challenges regarding the requirements of the new regulations. [10]

2.5 Oceania

The regulatory systems in New Zealand and Australia are stable with the Australian Therapeutic Goods Administration (TGA) and the MedSafe as their regulatory authorities. The impact of the harmonization group Global Harmonization Task Force (GHTF), which is now replaced by the International Medical Device Regulators Forum (IMDRF), can be identified easily since the registration requirements are aligned with their principles and guidelines. [11]

3 Harmonization of regulatory requirements

When regulatory authorities started describing requirements, harmonization groups were formed trying to streamline these different requirements. One of the most important harmonization groups would be the already mentioned IMDRF.

It is a voluntary group which was founded in 2011 to continue the work of the GHTF, founded in 1992. Current members of the IMDRF are Australia, Brazil, Canada, China, EU, Japan, Russia, Singapore, South Korea and the USA. Official observer is the WHO, which is not involved in the decision-making procedure though. Also, there are Affiliate Organizations which may be invited for Management Committee meetings for observations, which are the Asia-Pacific Economic Cooperation (APEC) LSIF Regulatory Harmonization Steering Committee, the AHWP the PAHWP. The Committee of the IMDRF identifies specific activities in their work plan and establishes working groups. These working groups develop technical documents and guidelines. [12]

Another harmonization group worth mentioning would be the ASEAN which is generally an international organization aiming the improvement of the economic, political and social collaboration of the member states. In the medical device sector it aims to harmonize the registration procedure of medical products in the area of Southeast Asia by establishing a medical device directive (AMDD) effective for all member countries, which are Brunei, Cambodia, Indonesia, Laos,
Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam. [7, 8]

4 Conclusion

The field of medical device market placement is constantly changing. Access to affordable high-quality medical products is only possible by establishing regulatory authorities, which define smart regulations and perform pre- and post-market controls and registration requirements, which include a realistic implementation of manufacturers. Manufacturers should therefore be supported by regulatory authorities during the registration procedure with guidelines as well as harmonization activities.

Manufacturer should describe a proper technical dossier, where the technical dossier should at least include the requirements of harmonization groups. Additionally, a proper QMS is not only almost obliged for market placement but of course for the company itself.

Author Statement
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