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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

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Analyse weltweiter regulatorischer Anforderungen an Medizinprodukte und In-vitro Diagnostika zur Ableitung eines effizienten Registrierungsprozesses für Medizintechnik-Hersteller

Zusammenfassung

Gegen Ende der Produktentwicklung eines Medizinprodukts werden Hersteller mit Registrierungsanforderungen konfrontiert. Die Globalisierung leistet einen wesentlichen Beitrag dazu, dass Produkte auf dem internationalen Markt in Verkehr gebracht werden. Diversitäten der lokalen Anforderungen stellen eine Herausforderung vor allem für Klein- und Mittelunternehmen dar, deren Ressourcen oft eingeschränkt sind. Harmonisierungsgruppen haben es sich zur Aufgabe gestellt, diese nationalen Diversitäten zu entzerren und einheitliche Zulassungsmöglichkeiten zu definieren. Ein effizienter Zulassungsprozess, der auf lokale Anforderungen eingeht und diese übersichtlich darstellt, hilft dabei, die wertvollen Ressourcen zu sparen.

Schlüsselwörter: Registrierung – Medizinprodukt – Harmonisierung – Inverkehrbringen – Prozess

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

Towards the end of the development phase of medical products manufacturers are confronted with registration requirements. Due to globalisation, products are placed on the international market. Diversities of local requirements result in a challenge especially for small and medium sized companies, whose resources are often limited. Harmonization groups have taken up the task to equalize these diversities and to define consistent registration requirements. An efficient procedure of registration, which reacts on local requirements and displays them clearly, helps saving those valuable resources.

Keywords: Registration – medical product – harmonization – market placement - procedure

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Abbrevations

AHWP	Asian Harmonization Working Party
AIMD	Active implantable medical devices
AIMDD	Directive on active implantable medical devices (EU-90/385/EEC)
ANMAT	“Administracion National de Medicamentos, Alimentos y Tecnologia Médico”
ANSM	“Agence Nationale de Sécurité du Médicament et des produits de santé”
ANVISA	“Agência Nacional de Vigilância Sanitária”
APEC	Asia-Pacific Economic Cooperation
ASEAN	Association of Southeast Asian Nations
BASG	„Bundesamt für Sicherheit und Gesundheit“
BGMP	Brazilian good manufacturing practice
CDSCO	Central Drugs Standard Control Organization
CFR	Code of Federal Regulations
COFPRIS	“Comision Federal para la Proteccion contra Riegos Sanitarios”
DoC	Declaration of Conformity
EEC	Eurasian Economic Comission
EU	European Union
FDA	Food and Drug Administration
FSC	Free Sales Certificate
GHTF	Global Harmonization Task Force
GMP	Good manufacturing practice
IMDRF	International Medical Device Regulators Forum
IFU	Instructions for use
ISO	International Organization for Standardization
IVD	In-vitro diagnostic medical device
IVDD	Directive on in-vitro diagnostic medical devices (EU-98/79/EC)
IVDR	Regulation on in-vitro diagnostic medical devices (EU-2017/746)
JGMP	Japanese good manufacturing practice
LoA	Letter of Authorization
MD	Medical devices
MDD	Directive on medical devices (EU-93/42/EEC)
MDR	Regulation on medical devices (EU-2017/745)

MDSAP	Medical Device Single Audit Program
NMPA	National Medical Product Administration
OSMD	Open source medical device
PAHWP	Pan African Harmonisation Working Party
PIP	Poly Implant Prothese
PMA	Pre-market approval
PMDA	Pharmaceutical and Medical Devices Agency
PMN	Pre-market notification
PoA	Power of Attorney
PoC	Point-of-Care
QMS	Quality Management System
RCP	Regulatory Clearance Plan
SOP	Standard Operation Procedure
STED	Summary of technical documentation
TGA	Therapeutic Goods Administration
TU	Technical University
UDI	Unique Device Identification
USA	United States of America
WHO	World Health Organization

Comments

Medical products in the sense of the presence thesis are products which are medical devices or in-vitro diagnostic medical devices defined in the regulations of the European Union for medical devices (2017/745) and in-vitro diagnostic medical device (2017/746)

1 Introduction

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. Therefore governments enact laws, directives and regulations. Nevertheless, these regulations can impede innovation and create trade barriers which result in an adverse effect on national economies. [1]

One product group that has major influence on the population`s health sate is that of medical products. According to the regulation for medical devices (MDs) of the European Union (EU) (2017/745-MDR), a medical device is as defined in article 2 (1):

> *"[…] any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:*
> - *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
> - *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
> - *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
> - *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.*
>
> *The following products shall also be deemed to be medical devices:*
> - *devices for the control or support of conception;*
> - *products specifically intended for the cleaning, disinfection or sterilization."* [2]

The regulation for in-vitro diagnostic medical devices (IVDs) of the EU (2017/746-IVDR) describes these products in article 2 (2) as:

> *"[…] any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, piece of equipment, software or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information on one or more of the following:*
> *(a) concerning a physiological or pathological process or state;*
> *(b) concerning congenital physical or mental impairments;*
> *(c) concerning the predisposition to a medical condition or a disease;*
> *(d) to determine the safety and compatibility with potential recipients;*
> *(e) to predict treatment response or reactions;*
> *(f) to define or monitoring therapeutic measures. Specimen receptacles shall also be deemed to be in vitro diagnostic medical devices;"* [3]

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. [4]

Market placement means: *"the first making available of a device, other than an investigational device, on the Union market"* [2]. After determining the countries, where market placement shall be conducted, one will realize, that there are different national requirements that must be fulfilled, before the product can be sold on the various markets. A registration concept is necessary to avoid waiting periods and to find enough resources for the handling of these procedures. [4]

The foundation of regulatory requirements is often a risk classification. This risk-based approach tries to focus the effort of control as well as design of medical products to those which have greater impact on the health state of patients, users or the society. Thus, before any regulatory requirement is investigated, if existent, a classification system must be identified.

Then regulations for market placement of medical products can be determined. These are regulations, directives and laws, which define requirements amongst other things for quality management systems (QMS), usability, risk management, design and development, software, verification and validation or operations.

The International Organization for Standardization (ISO) publishes documents, which define requirements, specifications, guidelines or characteristics to ensure that materials, products or processes fit their purpose. Complying with these standards, which provide the current state of the art, covers some requirements of regulations. The most important standards for medical products are: EN ISO 13485 which describes requirements for the QMS, the EN ISO 14971, which defines proper risk management, EN IEC 62366 covering usability aspects, the EN IEC 62304 defining requirements for software of medical products and the EN ISO 14155 dealing with clinical evaluations. [4, 5]

Also other nations provide guidelines or standards including testing methods and acceptance criteria for product development and design with the chance of product registration. Records must be created for regulatory authorities to control the effectiveness of these procedures, which are supported by standards or guidelines for practical implementations. [6]

The duality of regulatory requirements, which is on the one hand safety of the population and in the other hand trade barriers, leads to the formation of harmonization groups. They try to engage these two characteristics to improve the efficacy of national economies and to sustain its competitiveness without risking sacrificing the populations’s wellbeing. National regulatory requirements of different countries vary from being non-existent at all to being very demanding thus requiring a couple of years

for completion of the registration. Streamlining these registration activities can minimize the negative impact on innovation in the medical device sector. [1]

Manufacturers can streamline regulatory requirements by an efficient registration procedure to manage national variations. Clear inputs and outputs as well as responsibilities for each procedural step avoid nonconformities. This kind of procedure is drafted by the example of an IVD manufactured in Austria.

The e|1 Analyzer is the first product to be placed on the market by EXIAS Medical. This product is intended for the measurement of the electrolytes Sodium (Na^+), Potassium (K^+), Calcium (Ca^{2+}) and Chloride (Cl^-) as well as pH and Hematocrit (Hct). Neither the e|1, nor any of its component come in contact with patients and it is dedicated for use in laboratory and Point-of-Care (PoC) testing, that does not require referral to specialist facilities. All parameters are measured in human whole blood, serum, plasma, diluted urine and aqueous solutions. This intended use defines the in-vitro determination of physiological parameters derived from specimens of human bodies. Therefore the e|1 can be assigned to the product group of IVDs.

This product will be placed on markets all over the world after the registration on the European market is accomplished. Therefor regulatory requirements from all over the globe are reflected.

2 Scope

The scope of this Master Thesis is to determine different regulatory landscapes worldwide and investigate harmonization activities in the medical device sector to gain a solid knowledgebase of regulatory requirements for medical products.

The output of this thesis is a basic understanding of regulatory systems and compliance in the medical device sector and a Standard Operating Procedure (SOP) with a Regulatory Clearance Plan (RCP) as a main tool for registration activities for EXIAS Medical. The SOP shall be embedded within the QMS of the company. Schemes for registration procedures shall be identified for a unification of regulatory requirements and implemented into the registration procedure.

Therefore laws, regulations and directives as well as guidance papers, which should provide the current state of the art, are studied, to evaluate the existing registration opportunities and to derive a procedure, which should use similarities of the different registration procedures. Regulatory requirements for IVDs as well as MDs are gathered to gain an overview of the global regulatory landscape in the biomedical engineering sector. Furthermore, harmonization groups are studied to derive a trending for future registration activities.

In the chapter “Methods” the literature research is explained thoroughly to provide transparent information sources and repeatable results.

The chapter “Results” contains an objective listing of the collected data. Since regulatory systems are often based on a risk-based classification of products, first the different classification systems are described. This risk-based classification decides further registration activities requested by regulatory authorities.

Then to each country of interest regulatory requirements are listed and the current state of regulatory systems is drawn. The global market is grouped into Africa, North and South America, Asia, Europe and Oceania. The listing of the markets is alphabetical. Specific markets like the United States of America (USA), Canada, Brazil,

Russia, India, Japan, China, the EU, Australia and New Zealand were chosen to cover each region of the globe as well as additionally Argentina, Mexico, Indonesia, Philippines and Vietnam, representing important markets for EXIAS Medical. An important not here is, that registration requirements are always defined from the perspective of an Austrian manufacturer. Thus a clear focus on conformity assessment procedures inside the EU is put.

After that, harmonization groups, which have a significant impact on national regulatory requirements as well as on their future developments, are explained. The collected data is then practically implemented in the procedure of registration for the company EXIAS Medical.

Finally the registration procedure of the e|1 Analyzer contains registration relevant information for that product. The QMS of EXIAS Medical and the SOP “Product Registration” are described in detail as well as the RCP. The drafted documents are attached in Annex I and Annex II.

A deduction of trending and the analysis of the found results as well as the critical questioning of the gathered information is performed in the chapter “Discussion”. Classification systems are compared and an analogy of the different requirements worldwide is established. Current developments of the regulatory requirements of the EU are discussed with a clear focus on the changes the new regulations entail and their consequences for manufacturers. The role of harmonization groups within this developments is discussed.

All of that leads to a final explanation for designing the SOP as well as the RCP and a fundamental knowledge of regulatory systems all over the world.

3 Methods

This chapter contains a comprehensive and complete documentation of the literature research to provide traceability of the various information's sources referred to in this Master´s Thesis. Therefore the used strategies of finding relevant information is documented.

To start a practical literature research, a draft of the thesis was necessary. With this draft the main chapters that were researched on, were defined, to get an overview and to derive a strategy for the collection of data.

At the beginning of the literature research the current regulatory requirements in Austria were determined. Since Austria is a member state of the EU, the currently effective directives and regulations provided by the BASG ("Bundesamt für Sicherheit und Gesundheitswesen") were studied, to get familiar with regulatory systems.

Then the literature research was started in relevant databases for scientific papers. Searching in PubMed the following keywords were used: "harmonization", "medical devices", "registration" and "regulatory requirements". The filter was set for publications not older than five years, since there is a continuing change of requirements. The search led to an amount of hits lower than 15 mostly related to specific products like companion diagnostics, inhaled combination products or drug eluting products. A general overview of current regulatory requirements could not be created by that data's evaluation, but trending and the development of developing countries was possible.

To get more relevant data for registration requirements, a general search engine was stressed as well as the TU Graz library and Google Scholar. Next to more interesting papers about regulatory systems in developing countries also information about regulatory requirements on country level were found. Again keywords like "medical device registration", "in-vitro diagnostic medical device registration" were used in combination with countries of relevance. Here the above mentioned keywords led to a great amount of hits, which were sorted out by evaluating the entities providing information. Entities with relevance were "Emergo", "World Health Organisation"

(WHO), homepages of the European Commission and of notified bodies or consultants of quality management systems and regulatory affairs.

The “Johner Institute” describes blogs informing about current regulatory developments all over the world. “TÜV Süd” as well as the company “Encotec” provide information especially regarding registration on the European market. A good source for data about current developments in the USA is the “greenlight guru”. “Qualtech medical device regulatory & CRO” delivers information mostly about the Asian regulatory systems. These entities were considered to be promising because of former experiences or quick and competent responses to asked questions.

At that point the WHO was identified as a promising source. Not only due to the fact, that it is an important harmonization group in the medical device sector, but since it provides papers from 2016 about regulatory systems of each country. In these papers for each country the main information about the national regulatory authority and, if applicable, classification systems for the products are drafted. These papers also offer links to homepages of national regulatory authorities which provided further information.

Also “Emergo” was detected as source for regulatory requirements at country level. An advantage of these papers was the design specifically for medical product manufacturers. Together with information provided by some regulatory authorities, the WHO papers, and the book “Anforderungen an Medizinprodukte – Praxisleitfaden für Hersteller und Zulieferer” a solid regulatory strategy of each countries could be drawn.

For information about future developments and to remain up to date during the research, newsletters were requested. These were of the “Johner Institute”, the “greenlight guru”, the “Emergo Group” and “Qualtech”.

Another involved party in the identification of regulatory requirements were distributors. Especially when it came to completing the RCP and creating the SOP of product registration, the distributors' information provided by each countries' distributor was relevant. Distributors provided lists of requirements customized for the e|1 Analyzer, which were compared to researched information in order to identify missing documents and to verify their statements.

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4 Results

4.1 Classification systems

Medical products range from a simple band aid to radiation emitting machines. Its sector is characterized by the close interaction of science and engineering and is growing with increasing numbers of complex products. Due to their high potential for harm and impact on humans as well as public safety, nations define regulations to control these products. [7]

A band aid does not need the same regulatory controls as a hip prosthesis. Consequently, to manage the complexity and variety of medical products and their requirements, regulatory authorities have implemented classification systems. 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. This classification results in 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. [8, 9]

To get even more adjusted regulatory requirements for each product, some nations distinguish between product groups and define risk classes for each. The most common distinction is made between MDs and IVDs. [3]
The legislation of the EU even goes further by defining isolated requirements for active implantable medical devices (AIMDs), which are devices intended to be totally or partially introduced into the human body or a natural orifice, intended to remain after the insertion. This additional distinction is reversed though by the latest update of the regulatory framework. [10, 11]

Taking a deeper look into the classification system of the EU it can be perceived that there is a risk-based classification for all product groups.
What must be anticipated here is, that there are currently two legal bases effective in the EU, resulting in different available classification schemes. One legislation was

defined in the 1990´s consisting of three directives: one for MDs (93/42/EEC-MDD), one for IVDs (98/79/EC-IVDD) and one for AIMDs (90/385/EEC-AIMDD). These directives will be definitely replaced in 2020 by the regulation for MDs (2017/745-MDR) and in 2022 by the regulation for IVDs (2017/745-IVDR), which became effective on May 25th 2017. A more detailed description will follow in the chapter 4.2.4.1, where the regulatory landscape of Europe is outlined.

According to the MDD, devices can be divided into 4 risk classes, class I, class IIa, class IIb and class III, where risk class III is associated with the highest inherited risk for users, patients or public health. Products of risk class I with measurement function or sterile ones, must fulfil additional requirements. The classification system is based on 18 rules described in Annex IX and by finding the applicable rule(s) for the product, a risk classification is possible. [12]

The MDR describes in total 22 rules in Annex VIII and, next to class I medical devices with measurement function or sterile ones, there are also requirements for class I medical devices, which are reusable surgical instruments. [2]

The classification system described by the IVDD distinguishes between devices which can be assigned to either List A or List B of Annex II of this directive, with products assigned to List A being products related to the highest risk. This classification has been remodelled by the IVDR where a rule-based classification system is introduced in Annex VIII resulting in the assignment of the products to classes A, B, C and D. Class D corresponds to the highest risk class. Seven rules help assigning products to each risk class. IVDs for self-testing have an isolated role and demand the fulfilment of more regulatory requirements in both, the directive and the regulation. The IVDR introduces another definition with the near-patient testing devices. They demand the fulfilment of more regulatory requirements too. [3, 13]

AIMDs are according to article 1 (2c) AIMDD [10] defined as:

> *"any active medical device which is intended to be totally or partially introduced, surgically or medically, into the human body or by medical intervention into a natural orifice, and which is intended to remain after the procedure;"*

These products do not earmark a risk classification, since the potential risk of these devices is already considered to be very high. In 2020 AIMDs will be regulated by the MDR, so technically the regulation provides a classification system for these products as well. [10, 2].

A four-tier based system, explained here using the regulations of the EU as an example, is rather common. Classification systems are not always rule based, but the result of 4 different risk classes is applicable for the following countries listed in table 1:

- Argentina
- Australia
- Brazil
- Canada
- Egypt
- European Union
- India
- Indonesia
- Japan
- New Zealand
- Russia
- South Africa
- South Africa
- Vietnam

table 1: Countries using a four-tier based classification system

Not only regulatory authorities define this kind of classification systems. Also guidance documents of harmonization groups define and support a four-tier based risk classification system. The ASEAN (Association of Southeast Asian Nations) as well as the GHTF (Global Harmonization Task Force), both being described more precisely in chapters 4.3.3 and 4.3.5, also define a rule and four-tier based classification system. [9, 14, 15]

The guidelines GHTF/SG1/N77:2012 for MD classification and GHTF/SG1/N045:2008 for the classification of IVDs, both published by the GHTF, distinguish between class

A, B, C and D, where class D defines products with the highest potential risk. The final evaluation of the risk can be done by applying 17 classification rules for MDs and 7 rules for IVDs. [9, 14]

The ASEAN defines the ASEAN Medical Device Directive (AMDD), which classifies MDs by the application of 16 rules and IVDs by the application of again 7 rules, which are defined in Annex II and Annex III of that directive. The final risk classes are again classes A, B, C and D for both product groups. [15]

Another possible classification system can be explained by the example of the United States of America (USA). Different to the EU, where the manufacturer classifies the product himself, the Food and Drug Administration (FDA), which represents the regulatory authority, classifies the product according to a three-tier based system. This classification is group-based, so by assigning the product first to a specific group the final classification is done, since each group is assigned to risk classes I, II, or III. Class I represents low risk products, and class III represents high risk products. For this assignment the FDA has defined 1700 product groups, which are classified. [4]

The three-tier based classification system is also used by the National Medical Product Administration (NMPA) of China and the regulatory authority of Mexico the “Comision Federal para la Proteccion contra Riegos Sanitarios” (Cofepris). Both regulatory authorities describe rules for their three-tire based classification systems [4, 16].

4.2 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. Weak regulation of medical products represent a major risk for the population. By prescribing regulations, 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. [6]

The WHO collected data on the regulatory systems at country level between 2015-2016. For each country, the WHO evaluated the state of the regulatory system by identifying specific characteristics such as the national regulatory authority, the definition of medical products, the medical product classification system, essential principles that must be fulfilled, conformity assessment procedures, clinical evaluations and post market controls. These factors are used to identify the current development of each country`s regulatory system. [17]

In the following chapter national regulatory requirements are depicted, with regard to the characteristics described by the WHO, to display the actual state of regulatory systems.

4.2.1 *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 MDs and 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, is depends on its intended purpose. If the product lies within the scope of curing, identifying or assisting the treatment of a specific 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. [7]

Regulatory bodies for medical products are existing with some exceptions (e.g. Rwanda), that have just begun to instigate actions towards the establishment of a Food and Drug Authority. Interestingly, most countries provide regulatory bodies for medicines. [7]

Where regulatory bodies are established, the national manufacturers are challenged by relevant procedures for receiving market clearance. Specific equipment or laboratory testing for evidence of fulfilling essential requirements, which is not possible due to the lack of trained personnel or laboratories, result in economic burdens. These are overcome more easily by manufacturers of industrial states that have access to laboratories with the necessary equipment as well as the needed personnel. [6]

Egypt serves as an example, where a regulatory body, the Central Administration of Pharmaceutical Affairs has been established, which oversees the medical device market. The homepage of that regulatory authority refers to the classification schemes of the EU’s MDD and states that there is a draft version of an own medical device regulation. But this regulation is not effective yet. Latest information said, that the effectiveness would begin in September 2018. Further information could not be found though, so it is not to be expected that they are operative yet.

Nevertheless according to the actual regulatory system all MDs to be imported require market approval in either the USA, the EU, Australia, Japan, Canada or New Zeeland and a Free Sales Certificate (FSC), instructions for use (IFU), a declaration of conformity (DoC) and clinical data or test reports supporting the safety and efficacy of the product. So, the Egyptian Ministry of Health is relying on the regulations of before mentioned countries. [18, 19]

South Africa represents an example for own regulations. Briefly it has passed into law the Medicines and Related Substances Amendment Act 14 of 2015. This Act includes a comprehensive regulatory framework for medical products, which did not exist before. Previously medical products were unregulated or if the product was an electronic one, registration was needed before its sale. The range of medical products of the new framework lies between a simple band aid to a magnetic resonance imaging scanner, segregated by a four-tier based risk classification. A government body outside of the public service was established for the oversight of medical products and medicines and vested with making decisions and to act through its board. This body shall control and manage the risk of medical products throughout their life cycle. [20]

Generally, in Africa pre-market activities, like audit visits at manufacturer sites to evaluate QMSs, are not conducted. Some pre-market testing of IVDs is done in local laboratories where other countries simply accept products approved by donor agencies. If products have already gained market approval in industrial states (EU, USA, Japan etc.), the registration procedure can be abridged.

The post-market control system is more reactive than proactive due to the absence of regulatory capacity. Still, for example in Tanzania and Uganda, investigations are undertaken, if problems are reported. In some cases, like Rwanda, post-market monitoring is conducted by programs against HIV/AIDS or tuberculosis but limited to IVDs with a corresponding detection function. [7]

4.2.2 *North and South America*

4.2.2.1 Argentina

Medical products in Argentina are controlled by the “Administracion National de Medicamentos, Alimentos y Tecnologia Médico” (ANMAT). The homepage of the regulatory authority has links to the applicable legislation disposition 2318-2002 regarding medical products. These legislations are presented in Spanish, what can be an obstacle for foreign manufacturers. A distributor for communicating with the authorities for any translation activities is necessary.

Dependent on the four-tier based classification system for medical devices, which is very similar to the European system described in the MDD (also 18 questions- based), different registration requirements must be met resulting in different registration duration. The distributor must pocess a Letter of Authorization (LoA) confirming that the distributor is allowed to import and register the product. A FSC is also required as well as some technical details regarding the product and information confirming the safety and efficacy of the product. A registration certificate is valid for 5 years after. [21, 22]

4.2.2.2 Brazil

The national regulatory authority in Brazil is the “Agência Nacional de Vigilância Sanitária” (ANVISA), who describes requirements for registration, control and monitoring of medical products in Decree 8077/2013. Dependent on the four-tier based classification of either MDs or IVDs, there are different registration procedures. MD risk classes are classes I-IV and IVD classes are I to IIIa, where class III are those with the highest risk and IIIa those for self-testing. There is the need for a registration holder in Brazil, who will represent the manufacturer and is responsible for the communication with ANVISA. Since all registration documents must be submitted in Portuguese, the Brazilian registration holder can also support its translation. [4]

Complying with Brazilian Good Manufacturing Practice (BGMP) is necessary for registration. The quality management system requirements are similar to the ISO 13485 and the CFR 21 (Code of Federal Regulations Title 21- Quality System Regulation) requirements of the US-american FDA. Still, for high risk medical products (MD: classes II, III and IV; IVD: III and IIIa), an examination of the quality management system by ANVISA auditors at the manufacturing site is required. [23]

Generally, ANVISA describes two pathways for registration of medical products. There is the so called “Cadastro route” for Class I and Class II devices and the more complex “Registro route” that is applicable for Class III and Class IV devices.

The Cadastro route requires less technical data and is a simplified registration procedure. A Letter of Authorization (LoA) is required as well as a technical dossier. This dossier includes a risk management file, an essential principle checklist and usability studies. The Cadastro registration does not expire, except if changes to the devices are undertaken, which must be reported to ANVISA before their implementation.

The Registro route requires, next to the requirements for a Cadastro registraion, a more detailed technical dossier including a satisfactory evidence of the product`s quality and safety by a pivotal clinical study. A registration is valid for ten years and reregistration activities must be started one year ahead. [24]

After market approval a post-market surveillance system must control products in the field and a vigilance reporting system must be installed by the manufacturer. [4]

4.2.2.3 Canada

The control of medical products in Canada is performed by Health Canada. Medical devices and IVDs are defined separately and for both a four-tier based risk classification exists. The legislation for medical product registration is the SOR/98-282. Canada does not need a local representative for the registration of medical devices. Manufacturers must take control of their own registration. [25, 26]

Except for low risk medical products, the QMS of the manufacturer must be certified according to the rules of the Canadian Medical Device Conformity Assessment System. This System is based on the ISO 13485 and extended by requirements of the Medical Device Regulation defined by Health Canada. The certification of the QMS must be conducted by an agency and an auditor, which are certified by Health Canada. Additionally, products of risk classes II, III and IV are published in a specific data base. Part of this QMS must be post-market controls, which include a vigilance system controlling the reporting of serious incidents to the authorities within a specific time frame. [26, 4]

On January 1st of 2019 Canada's transition deadline for the MDSAP (Medical Device Single Audit Program) passed. From that moment on, only MDSAP certifications for manufacturer`s QMS is valid for product registration. The MDSAP is described in detail in chapter 4.3.5. [27]

4.2.2.4 Mexico

Medical products in Mexico are ruled by the "COFEPRIS" which defines the "Ley General de Salud". A representative for communication with COFEPRIS and the control of the registration in Mexico must be announced.

Medical products are separated into six different product groups, which are classified into three risk classes. After submitting the registration application, the regulatory authority will classify the medical product. There is a distinction made between MDs and IVDs and both have individual classification system resulting in the assignment to class I, class II or class III of the product. Additionally class I low risk products are defined as products, that do not present any risk to physical harm and have no diagnostic or life supporting functions. All products other than class I low risk require a technical dossier and evidence for a QMS (ISO 13485 or similar). This must only be documented though. An audit at the manufacturer site conducted by COFEPRIS is not common.

If the product is already placed on a market like the USA, Canada, or Japan, the review process can be accelerated. A vigilance system is also required, since the regulatory authority in Mexico also performs post-market controls.

In 2018 COFEPRIS has updated the classification system of IVDs and related definitions. This update includes a set of rules for IVD classification instead of the generalization of the IVD products. Most IVDs are now class II products except for reagents and control material, which are risk class I and contrast media or radioactive substances, which are risk class III products. [28, 29, 30]

4.2.2.5 United States of America

In the USA the medical device industry is controlled by the FDA which defines demanding requirements in the Federal Food, Drug and Cosmetic Act that must be fulfilled by manufacturers. The FDA supports its regulations by publishing guidance papers for their practical application.

Generally the FDA does not differ between MDs and IVDs. For each product a marketing application must be created and approved before import is possible. Two procedures for market approval are possible: the 510(k) procedure also known as pre-market notification (PMN) or the pre-market approval (PMA). Which procedure is applicable for the product depends on the risk classification and the presence of an existing substantially equivalent product on the market.

Low risk devices are regulated by general norms related to the labeling, manufacturing and the post-market surveillance system. The safety and effectiveness of products must be evident and the FDA must be capable of countermeasures like recalls. Individual testing is not conducted by the FDA. [4]

Manufacturers of class I and II products, which can refer to a substantially equivalent product (i.e. predicate device) can follow the 510(k) procedure. Here three different 510(k) procedures are familiar. The traditional, special and abbreviated 510(k).

Special 510(k) means an accelerated procedure, which is applicable for minor changes of products, which are already approved for the US market. Market approval for products not registered in the USA yet or significant changes to already registered products require traditional 510(k) completion. A significant change in the understanding of the FDA is a change with consequences to the safety and effectiveness of the device of a major change of the intended use.

The abbreviate 510(k) procedure will be applicable, if guidance documents exist, special control are established, or the FDA recognizes relevant consensus standards. A comparison must be made to a product already placed on the U.S. market along with clinical data. It must be noted that bench and animal testing is mostly enough. [31]

After handing in the product dossier, the FDA reviews the documents. There are tools installed to accelerate the procedure, like an eCopy program for Medical Device Submission and a sort of incoming inspection of documents, which acts like a fast document verification for completeness. [4]

Complying with this act is quite a challenge for manufacturers. Statistically, 69% of the 510(k) applications are rejected, which is a major consideration in the resource planning of manufacturers. [32]

After the finalization of the 510 (k) procedure, the final review ot the FDA takes 90 days before market approval is gained. After this approval, the manufacture will be pointed to restrictions like GMP (Good manufacturing practice) or the annual registration and medical device reporting. A summary of the product dossier is evident on the database of the FDA. [4]

High risk medical devices (class III products and class II products, which cannot be registered by the 510(k) procedure) must gain pre-market approval (PMA). The PMA is the strictest procedure performed by the FDA where literature is examined as well as enough records for the safety and effectiveness of the product must be shown. Often experts are invited for evaluating the application. After publishing the application, interested parties are allowed to appeal against the decision.

After the manufacturer gains market clearance, a submission to a post-market-surveillance program within 30 days must be accomplished. The FDA needs 180 days to review the application. Due to feedback and questions by the FDA, this procedure can extent to a couple of years. [33, 4, 34]

The FDA also defines requirements for the QMS dependent on the risk classification. Class I products must comply with “Good manufacturing practice requirements” which are specified for the development, production, packaging, storage and installation of the product. An audit at the manufacturing site of class I products is not conducted.
All other devices must comply with the 21 CFR (Code of Federal Regulations Title 21) part 820, which is the US equivalent to the ISO 13485. It describes requirements for a complete QMS including control of documents and records, purchasing, development and production. For the practical implementation of the requirements, the FDA also provides guidance documents. [35]

4.2.3 *Asia*

4.2.3.1 China

The control of medical products and medicines is conducted by the National Medical Product Administration (NMPA). This regulatory authority is formally known as State Drug Administration (SDA), State Food and Drug Administration (SFDA) or China Food and Drug Administration (CFDA). The new nomenclature has been valid since the 1st of September 2018. The NMPA describes Decree No. 4 for the MD registration and Decree No. 5 for the IVD registration. [4, 36]

An authorized representative located in China, who is responsible for the communication during the registration and for vigilance reporting with NMPA, must be nominated. Additionally, to registration documents, like a letter of authorization (LoA) for the sales agent and the FSC, clinical studies, QMS evidence or special safety test reports can be necessary, dependent on the risk classification. The need for these additional requirements are contingent on already collected data to clinical studies or, if the product is already placed on another market with strict registration requirements like the USA or Canada. The QMS will be audited by the NMPA in case of class III products. Manufacturers of class II products can perform an audit by themselves, but the NMPA will then decide whether an additional audit at the manufacturer´s site is necessary or not. Class I products do not require any evidence for a QMS. A registration in China is valid for four years after the initial registration is completed. [4]

4.2.3.2 India

The national regulatory authority in India is the Central Drugs Standard Control Organization (CDSCO), who describes the Drugs and Cosmetic Act No. 23. For medical products. In 2017 India has updated its regulatory landscape by adapting the classification system as well as the registration procedure. [37]

The former classification system was based on the division of so called Non-notified IVDs and Notified medical products. Notified medical products were for example Blood

Grouping Sera, Bone Cements, Condoms, Heart Valves or IVD Devices for HIV, thus high-risk products. They required performance testing through the National Institute of Biologicals. An application form needed to be handed in by the manufacturer (Form 40) including technical device data, manufacturing facility information or an ISO 13485 certificate. Also the market approval in the USA, EU, Australia, Canada or Japan, including the country of origin was necessary. The registration of the device was valid for 3 years after completed initial registration. Non-notified IVD only needed an import permit. [38]

The new system came into force in January 1st 2018 including a complete restructuring of the classification system, which is from that moment on four-tier based. Still not every medical product requires registration. The CDSCO has created a list containing medical devices and IVDs and their corresponding risk class. An authorized agent for further interaction with the national regulatory authority must be selected, which shall be granted by the signature of a Power of Attorney (PoA). Some IVDs (testing of malaria, syphilis, cancer markers, etc.) must be tested by an accredited laboratory in India. An application (Form MD-15) must be filled in including technical data, the ISO 13485 certificate, clinical data, the proof of approval in US, EU, Australia, Canada or Japan is still necessary as well as market clearance for the country of origin. After a successful procedure of market approval, the registration will not expire, but a registration fee is mandatory every five years. [37, 39, 40]

4.2.3.3 Indonesia

In Indonesia the regulatory authority is the Directorate General of Pharmaceutical and Medical Devices. Also Indonesia is part of the ASEAN. Indonesia's government has signed the agreement to implement the AMDD in 2015 and therefore has already aligned its classification requirements to this directive. [41] [42]

There is a distinction made between MDs and IVDs. For both a four-tier based classification system is the basis for the technical dossier and its composition.
The classification of the product is part of the technical dossier. If the classification is not correct, this will be evaluated as a lack of the technical dossier. A distributor is

necessary for managing the registration in Indonesia. A FSC and a LoA for this distributor is required as well a QMS certificate. [42, 43, 41]

4.2.3.4 Japan

The national regulatory authority in Japan, that controls medical products, medicines, cosmetics and sanitary products, is the Pharmaceutical and Medical Devices Agency (PMDA). This authority is supported by a registered certification body, which is comparable to a notified body of the EU.

A marketing authoritzation holder in Japan is required, with the responsibility for vigilance reporting and as an interface between manufacturer and regulatory authority. This registration holder has to implement a QMS and apply for the license “Kyoka”. All documents must be submitted in Japanese. Dependent on the four-tier based classification system, requirements for the registration as well as the QMS are defined.

Three different procedures for market approval are applicable. There is the “Todokede” for class I products, the “Ninsho” for class II products and “Shonin” for class III and IV products. Class I products require evidence of the QMS of the registration holder as well as the manufacturer. Additionally to the requirements of class I products, class II products are certified by a regulatory certification body, who performs the product certification as well as the QMS audit according to Japan Good Manufacturing Practive (JGMP). Some notified bodies in the EU are accredited by the PMDA to perform such audits. Class III and IV products need approval by the PMDA. [4]

4.2.3.5 Philippines

Medical products in the Philippines are regulated by the Bureau of Health Devices and Technology. The island nation is a member state of ASEAN. There is a distinction made between MDs and IVDs regarding the registration application forms. Not all devices require registration. The FDA of the Philippines provides English information for foreign manufacturers including a list of medical devices and IVDs, which require registration [44].

By providing also English application forms for initial and renewal product registration, and relevant checklists, the regulatory authority is obliging to foreign manufacturers. [45, 46]

For the registration, a notarized application form for registration of the distributor, the FSC and a notarized ISO 13485 certificate must be handed in. Also, a product dossier, including risk analysis, a list of raw materials, stability test data, labeling and the intended use must be handed in. [47, 48]

4.2.3.6 Russia

In Russia medical products are controlled by the Federal Service on Surveillance ("Roszdravnadzor") who distinguishes between MDs and IVDs. Both groups are classified according to their risk by a four-tier based system, similar to the EU classification according to the MDD with risk class I, class IIa, class IIb and class III determined by applying those rules. Dependent on this risk classification, there are slightly different requirements that must be met.

All manufacturers must announce an authorized representative to coordinate with the regulatory authority and to translate applicable documents, since all registration documents must be handed in in Russian. Then existing test reports must be sent to a local authorized laboratory, which will determine further required tests there. After that an import permit for product samples for the tests must be gained. Afterwards products can be sent to Russia. In the meantime a technical dossier must be prepared including technical information, an ISO 13485 certificate and, if applicable, clinical studies. A notification of these certificates is necessary.

For class I products, the registration is eased, since the review of the technical dossier is not conducted as thoroughly as for other products and by the not required Expertise Center review and clinical trials conducted in Russia, which is necessary for class IIa, IIb and III products. After the dossier is reviewed and accepted, a registration certificate is handed out by the regulatory authority, which does not expire. Afterwards the Russian representative must apply for a Declaration of Conformity (DoC) certificate.

After receiving that final certificate, the DoC must be marked on the product as well. [49, 50]

4.2.3.7 Vietnam

In Vietnam the national regulatory authority is the Department of Medical Equipment and Health Works. Vietnam is also a member state of the ASEAN. There is no distinction made between MDs and IVDs and a four-tier based risk classification (classes A, B, C, D) is implemented and described by a new legislation,which became effective in July 1st 2016. This legislation defines the need for registration of medical products. Before that, only import permits were necessary. For the registration international certificates like the ISO 13485, the CE-marking of conformity and US-FDA approval is recognized. A FSC is required as well as a technical dossier and a certified QMS. [51]

4.2.4 Europe

4.2.4.1 European Union

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 MDs (93/42/EEC - MDD), AIMDs (90/385/EEC - AIMD) and IVDs (98/79/EC - IVDD). For AIMDs and MDs complementary directives were published in 2007 to complete their regulatory requirements. The European Commission supports the directives by guidance papers, the so called MEDDEV documents. These documents are created in study groups with members of the European Commission, notified bodies, and representatives of the medical device industry, regulatory authorities and lobbyists. Even though the requirements are harmonized, there are still national characteristics that must be considered (e.g. national language requirements). [4, 52]

An important role in conformity assessment procedures apply to notified bodies. These are private institutions, which are authorized by the state to perform evaluations and examinations at the manufacturers` site to confirm, that their conformity assessment procedure complies with applicable standards. The notified body can be chosen by manufacturers, but as soon as one notified body is chosen, it is forbidden to enter into a contract with another one. [53]

As already mentioned in chapter 4.1, there is currently a transition period in the EU where additionally to the directives, two regulations are effective. In May 2017 these regulations became effective to replace the before mentioned directives. [11]

Generally, 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. [54]

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 AIMDs. 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 IVDR as well as the MDR have introduced additional product groups, which require higher control. The MDR has defined requirements for class I MDs which are reusable surgical instruments and the IVDR has added the definitions of near-patient testing device and companion device. [11]

To ease the transfer to the new regulatory framework, transition periods were defined. On the 26th of May 2020 all products regulated by the MDR must be placed on the market according to that new regulation. For manufacturers of IVDs the transition period is until the 26th of May 2022. [4, 55, 54].

Technically, manufacturers currently can choose whether they want to certify their product according to the regulation or the directive. Practically, the notified bodies must be notified according to the regulation first, before any action towards the certification of products can be taken.

The tightening of this regulatory system was not a proactive measure though. The procedure for new regulations was encouraged by serious incidents revealed in 2010. The French regulatory authority (Agence Nationale de Sécurité du Médicament et des produits de santé -ANSM) found out that a manufacturer was producing breast implants not using the approved specified silicone. [11]

Worldwide approximately ten thousand women were supplied with that nonconforming product by the French company Poly Implant Prothese (PIP). Many implants ruptured leading to complaints. After an audit of the ANSM at the manufacturer site, the product was withdrawn from the market. Not only was the manufacturer confronted with legal consequences, also the notified body certifying the implants (TÜV Rheinland), came

in the focus of the prosecutors. In November 2011 the first women died because of the consequences of receiving harmful implants. [56]

Due to arousing public interest the European Commission was forced to initiate immediate actions by conducting unannounced audits at manufacturer's sites and joined audits at notified bodies which led to closing half of the notified bodies. Another measure that was taken, was publishing the implied regulations. [11]

These regulations also describe reinforced requirements for notified bodies. A Joint-Assessment-Team shall perform the notification audits. These teams consist of two experts of other member states of the EU as well as one expert of the European Commission. A waiting period of 1.5 year for the notification of the first notified body is expected, which results in the first available notified body for the new regulations at the earliest in the second half of 2019. [11]

Returning to regulatory requirements in the EU, for each product group a technical documentation must be created, which also identifies essential requirements or general safety and performance requirements, which must be fulfilled, dependent on their risk classification. Next to these requirements, a conformity assessment procedure must be completed and a post-market surveillance system must be implemented successfully for market approval. This post-market surveillance system must include a vigilance system that assures proper vigilance reporting in case of serious incidents. For MDs and AIMDs a clinical study must be performed. IVDs require a performance evaluation as evidence for its safety and effectiveness. [4]

For each product group the possible conformity assessment procedures are described in the following: firstly for AIMDs, than for MDs and finally for IVDs.

As already mentioned, AIMDs inherit high risk. So there is no risk classification applicable. The possible conformity assessment procedures described in article 9 in the AIMDD are depicted in figure 1. The numbers in the orange circle refer to the directive's Annexes.

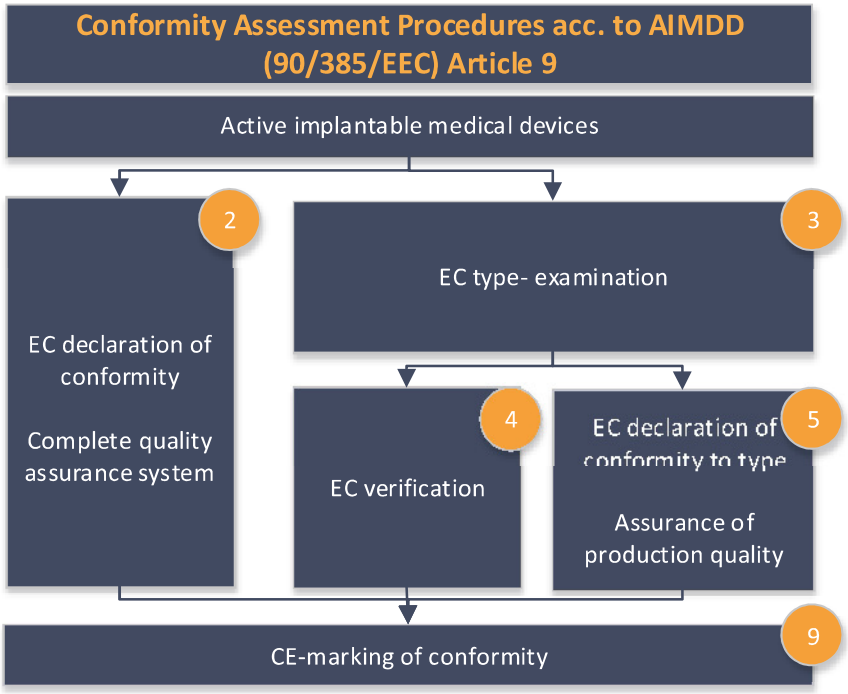


figure 1: Conformity assessment procedures acc. to AIMDD

Manufacturers of AIMDs can perform the EC declaration of conformity according to Annex 2 including the evidence of a complete quality assurance system. This quality assurance system includes a post-market surveillance system, naming of quality objectives, listing of applied standards, clinical data and if applicable sterilization methods. Also manufacturers can perform the EC type-examination described in Annex 3. In a type-examination the notified body observes a representative product sample. Type-examinations must be coupled with either the EC verification drafted in Annex 4, which is testing of statistical product lots, which are performed by notified bodies. Otherwise the EC declaration of conformity of Annex 5 including the assurance of production quality is possible in combination with the EC type-examination. That includes the documentation of a quality assurance system and especially the quality control of the production.

For MDs the MDD describes in article 11 the following conformity assessment procedures depicted in figure 2 applicable to each risk classification.

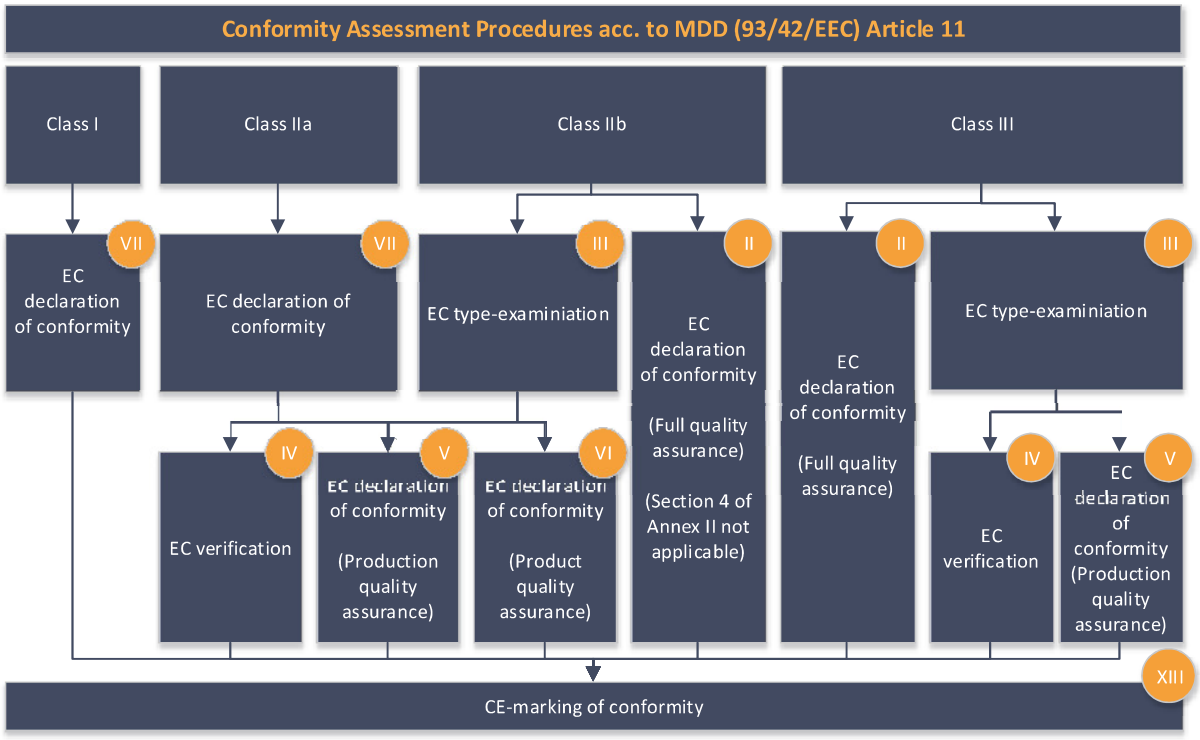


figure 2: Conformity assessment procedure acc. to MDD

Manufacturers of class I MDs must conform an EC declaration of conformity described in Annex VII. This includes requirements for a technical documentation and post market surveillance system. The complementary directive 2007/47/EC permits the conformity assessment procedure according to Annex II excluding section 4 for manufacturers of sterile class I MDs as well as class I MDs with measurement functions. This conformity assessment procedure is providing evidence of a full quality assurance system with evidence of product design documentation, clinical studies, evidence of design verification and if applicable sterilization methods. Section 4 contains the examination of the product's design. [12, 57]

For class IIa devices the conformity assessment procedure according to Annex VII is also applicable, but additionally Annexes IV, V or VI must be fulfilled. Annex IV describes the EC verification. Annex V is an EC declaration of conformity with a quality assurance of the production, whereas Annex VI list requirements for the EC declaration of conformity including product quality assurance. This means the evidence for quality controls and procedures of product release including the final inspection. Another possible conformity assessment procedure for IIa manufacturers is the EC declaration of conformity described in Annex II except for section 4. Annex II except for its section

4. This procedure is possible for manufacturers of class IIb MDs too. Other than that, an EC type-examination according to Annex III followed by either the fulfillment of Annex IV, V or VI is possible.

Risk class III MDs require the fulfillment of Annex II or III, where the type-examination must be coupled with either the EC verification described in Annex IV or the EC declaration of conformity set out in Annex V. [12]

The MDR describes possible conformity assessment procedures in chapter five section 2 article 52 dependent on the devices' risk classification (see figure 3):

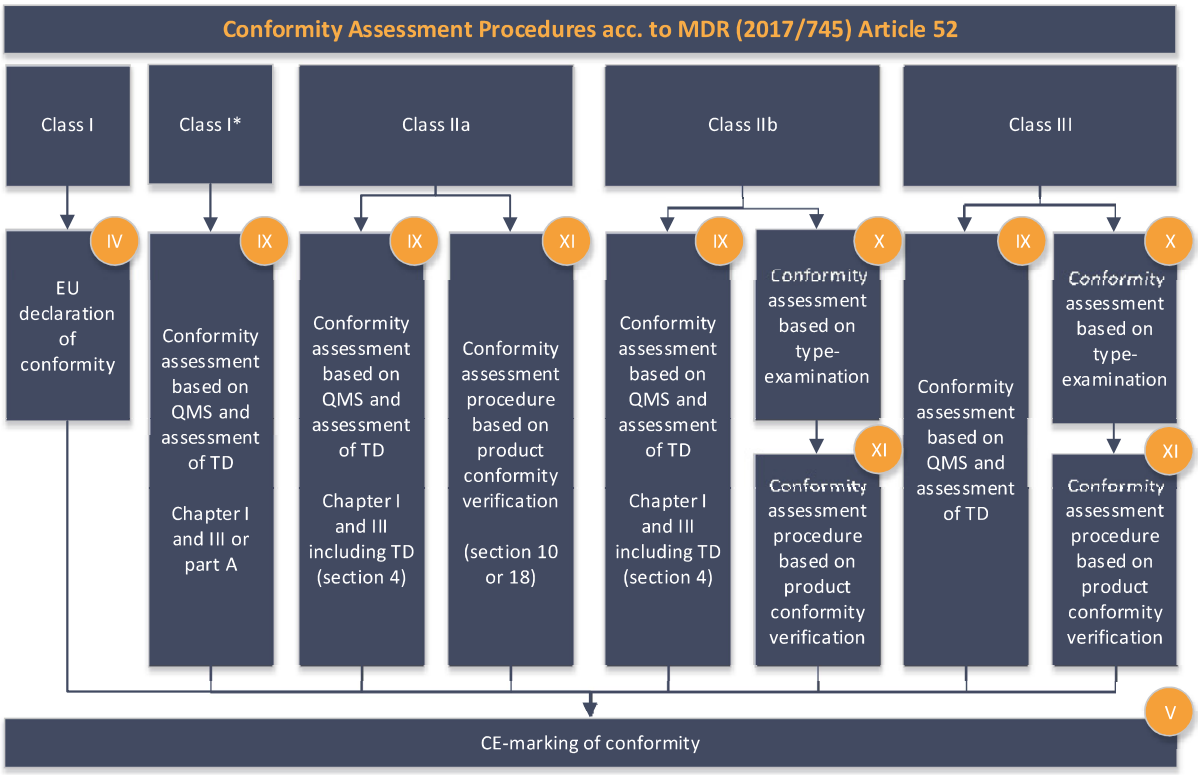


figure 3: Conformity assessment procedure acc. to MDR

For the market placement of class I devices, an EU declaration of conformity according to Annex IV must be drawn up, which includes the device's risk classification, the UDI device identification number and references to common specifications. If class I MDs include a measurement function, are sterile or reusable surgical instruments, the conformity assessment procedure´s chapters I and III defined in Annex IX or part A of

Annex IV is applicable. Chapter I and III are requirements for the QMS and administrative provisions and part A of Annex IV includes additional information, that must be provided for the UDI database.

Manufacturers of class IIa MDs shall perform either the conformity assessment outlined in Annex IX (chapters I and III including section 4) or section 10 or 18 of Annex XI. These sections include the check of technical documentation and a batch inspection.

Possible conformity assessment procedures of class IIb devices are the conformity assessment based on type examination outlined in Annex X coupled with a product conformity verification according to Annex XI. As for class IIa devices, the conformity assessment based on QMS and assessment of the technical documentation is applicable, but only chapter I and III including section 4.

Manufacturers of class III MDs shall perform either the conformity assessment according to Annex IX in its full extent, or the conformity assessment procedure according to Annex X coupled with the product verification defined in Annex XI.

Possible conformity assessment procedures for manufacturer of IVDs are listed in the in article 9 of the IVDD and depicted in figure 4. [2]

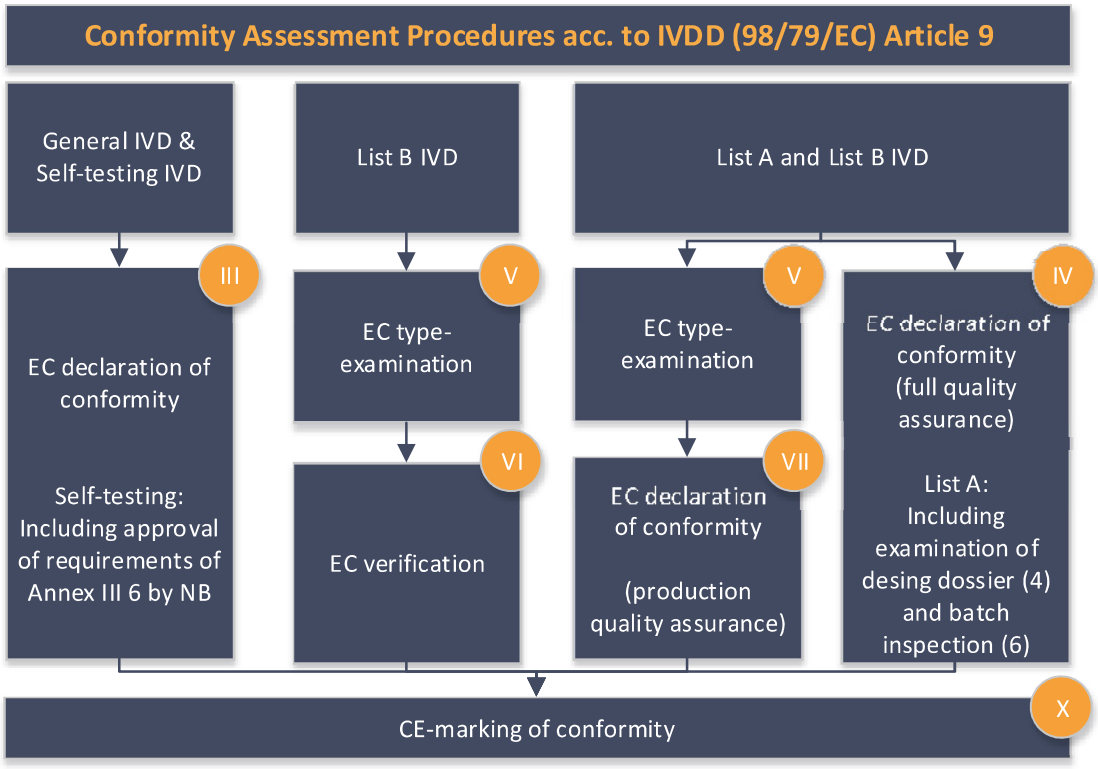


figure 4: Conformity assessment procedures acc. IVDD

Manufacturers of General IVDs must perform an EC declaration of conformity according to Annex III. This Annex demands preparing technical documentation and a post-market surveillance system. If the IVD is a self-testing device, additional approval of the requirements in section 6 must be fulfilled, that demands tests for the usability of the product design for lay persons. Other than that, manufacturers of self-testing devices can also perform the conformity assessment procedures applicable for List A and List B IVDs.

List B products must follow the procedure described in Annex IV, that describes requirements for a quality assurance system. Otherwise Annex V, a type-examination, can be coupled with either the EC verification set out in Annex VI or the procedure relating to the EC declaration of conformity set out in Annex VII which includes production quality assurance.

List A products must follow the procedure of the EC declaration of conformity set out in Annex IV including the inspection of a design dossier and a batch inspection. Otherwise the procedure relating to the EC type-examination set out in Annex V

coupled with the procedure relating to the EC declaration of conformity set out in Annex VII. [13]

The IVDR describes in chapter V, section 2, article 48 the following conformity assessment procedures depicted in figure 5 applicable to each risk classification.

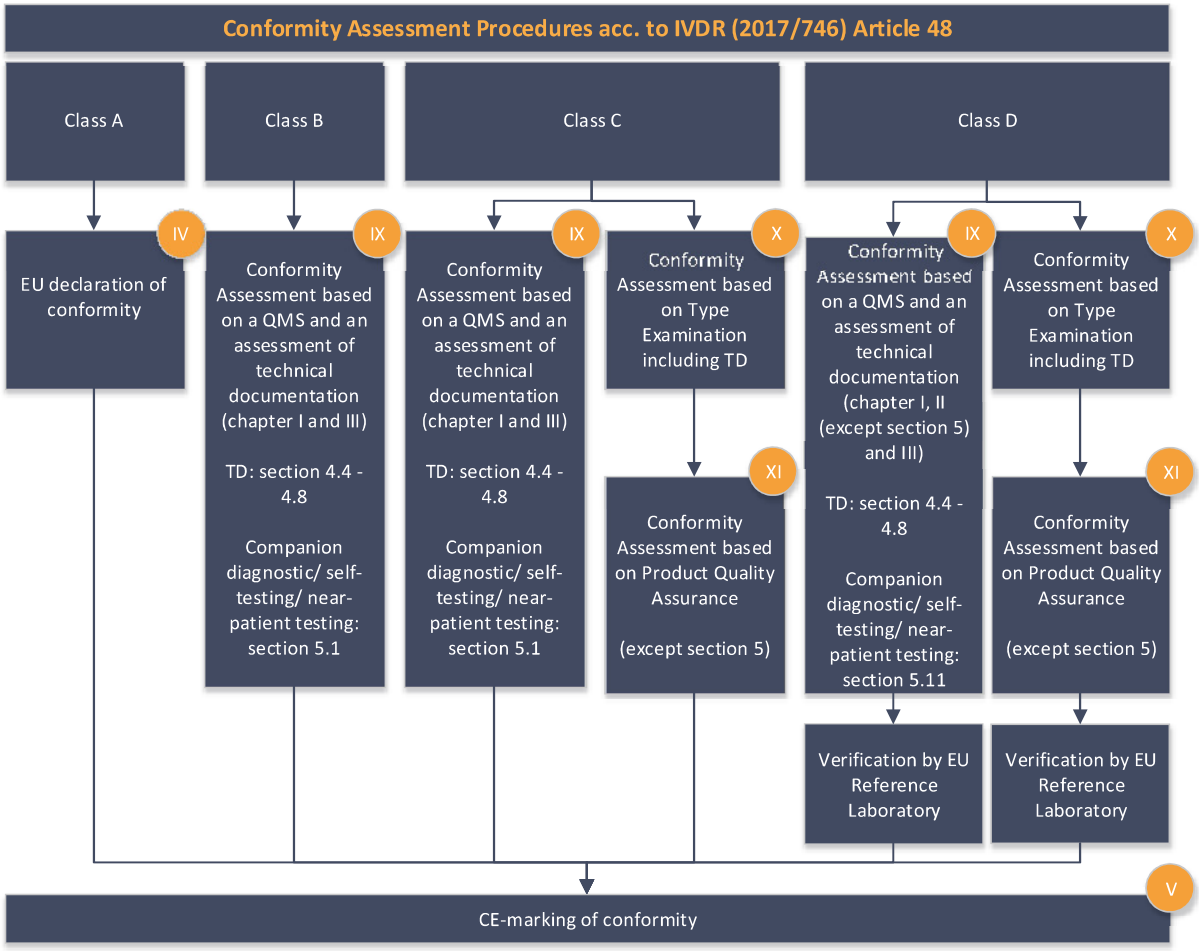


figure 5: Conformity assessment procedure acc. to IVDR

For the market placement of class A IVDs an EU declaration of conformity according to Annex IV is applicable.

Manufacturers of class B or C devices must perform the conformity assessment procedure according to chapters I and III in Annex IX based on an QMS including the assessment of the technical documentation as specified in its sections 4.4 to 4.8.

For class B or C devices which are used for near-patient or self-testing or companion diagnostics, the assessment of the technical documentation, set out in section 5.1 of Annex IX, must be conducted, which includes the assessment of the technical documentation by an application at the notified body.

Manufacturers of class D device must perform the conformity assessment according to chapters I, II (except for section 5) and III of Annex IX. Chapter II including the technical documentation assessment of the notified body. If the device is for near-patient or self-testing or a companion diagnostic, the assessment of the technical documentation set out in section 5.1 of Annex IX must be conducted as well.

Manufacturers of class C or D devices can also choose the conformity assessment according to Annex X, the type-examination, coupled with the conformity assessment as specified in Annex XI, product quality assurance, except for section 5 of this Annex, which defines batch examinations. [3]

Not every medical product requires a notified body for the conformity assessment procedure. For low-risk medical products, the manufacturer can prepare a self-declaration of conformity. These low-risk products are class I MDs (acc. to MDD or MDR) or General IVDs (acc. to IVDD), or class A IVDs (acc to IVDR). [12, 13, 2, 3].
As soon as the class I MD has a measuring function or is sterile, a notified body is again necessary for the conformity assessment procedure. The same applies to IVDs for self-testing, near-patient testing or companion diagnostics.

After completing the conformity assessment procedure, manufacturers are allowed to affix the CE-marking of conformity. Any product which lies in the scope of an EU directive or regulation must have a CE-marking, if it is to be placed on the European market. With this marking the manufacturer, conforms that the product complies with the applicable directives, regulations and norms of the EU. If a notified body is involved in the conformity assessment procedure, the CE-marking of conformity must be accompanied by the identification number of that notified body. [58, 13]

4.2.4.2 Switzerland

Switzerland, being in the center of Europe and surrounded by EU member states, has taken over the EU system of compliance assessment and certification based on bilateral agreements. The responsible agency for medical products in Switzerland is the Swiss Agency for Therapeutic Products, Swissmedic. Also international norms are recognized like in the EU and a CE-marking of conformity is obligatory for a product to be placed on the market. One difference lies in the wording for notified bodies, which are called conformity assessment bodies in Switzerland. [59, 60]

4.2.5 Oceania

4.2.5.1 Australia

The national regulatory authority in Australia is the Australian Therapeutic Goods Administration (TGA). Australia played an important role in the former GHTF harmonization group and therefore the registration requirements are aligned with their principles and guidelines. There is a distinction made between MDs and IVDs and AIMDs and a risk classification, which is four-tier based, for the IVDs and MDs. Since the Australian regulatory system is very similar to the EU regulatory framework, the TGA also accepts notified body CE-marking certificates, but in some cases additional reviews are conducted. An Australian Sponsor must be selected, who will manage the communication between the TGA and the manufacturer including post-market surveillance activities. A proper vigilance system must also be installed. [61]

In 2012 harmonization activities were started towards New Zealand by forming one regulatory authority for medical products, but in 2014 both Ministers of Health published a statement that costs would not be compensated by the benefits. Nevertheless, a close collaboration will persist. [62]

4.2.5.2 New Zealand

The national regulatory authority in New Zealand, MedSafe, dictates the listing of the product in the MedSafe`s Web Assisted Notification of Devices (WAND). Therefore, documentation proving the safety and effectiveness of the product must be provided. Like in Australia there is a four-tier based classification system installed which is similar to the classification system in the EU. One major difference is, that there is no distinction made between MDs and IVDs, but between MDs (including IVDs) and AIMDs. The risk classes are class I, class IIa, class IIb, class III and class AIMD.
A distributor must be selected for the listing of the product as well as post-market surveillance activities. [61]

4.3 Harmonization groups

After listing the different national regulatory requirements worldwide, it can be understood, that the effort to fulfilling each requirement is very high. The description of the requirements for medical products started in the 1980s. Since then more and more countries have started to define specific regulatory requirements for the registration of medical products on their markets. [1]
At the same time harmonization groups have formed all over the world to decrease the resulting trade barrier by easing the procedure of product registration for manufacturers by unifying the requirements. By the creation of one technical dossier, the regulatory requirements of many countries should be fulfilled. [8]
The most relevant harmonization groups are described in the following chapter.

4.3.1 Pan African Harmonisation Working Party

The Pan African Harmonisation Working Party (PAHWP) is a voluntary body, founded in 2013 and prioritizes its activities on the access to safe and affordable medical products, especially IVDs. Point-of-care testing devices are adjudged to save many lives by stopping the spread of infectious diseases (e.g. AIDS/HIV, malaria, tuberculosis, etc.). Tests of products shall be effective and safe to minimize costs and delays, allowing a quick access to affordable products. The PAHWP recommends ways of harmonization by a common registration file, a standard four-tire based classification, a single auditing program for QMSs and a mutual recognition of clinical evidence.

Member states are the East African Community (Kenia, Uganda, Tanzania, Burundi, Ruanda and South Sudan), Ethiopia, Nigeria and South Africa and the London School of Hygiene & Tropical Medicine. Official partners of this organization are the German International Co-operation, the African Society for Laboratory Medicine and the WHO. [63]

4.3.2 *Asian Harmonization Working Party*

The Asian Harmonization Working Party (AHWP) is a non-profit organization and founded in 1996-1997 by regulatory affairs professionals due to the growing interest in harmonizing the regulatory requirements in Asia. In 1998 the GHTF started supporting this non-profit organization. Current members are Brunei Darussalam, Cambodia, Chile, Chinese Taipei, Hong Kong SAR (China), India, Indonesia, Jordan, Kazakhstan, Kingdom of Bahrain, Kingdom of Saudi Arabia, Republic Korea, Laos, Malaysia, Mongolia, Myanmar, Pakistan, People´s Republic China, Philippines, Republic of Kenya, Singapore, South Africa, State of Kuwait, Sultanate of Oman, Tanzania, Thailand, United Arab Emirates, Vietnam, Yemen and Zimbabwe.

The organization provides guidance papers for QMS, Adverse Event Reporting and it refers to the MDSAP assessments, which will be described further on in connection with the IMDRF (see chapter 4.3.5). [64]

4.3.3 *Association of Southeast Asian Nations*

The Association of Southeast Asian Nations (ASEAN) is 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. The AMDD consists of 24 articles, which describe inter alia, Essential Principles, Classification rules of medical devices and IVDs, conformity assessment procedures, and labeling requirements. Its member countries are Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Vietnam. [41, 65]

The harmonization of the legislation in these countries will lessen the effort for product registration in the member country. By performing the registration once in a member state, the document dossier or rather the registration will be also recognized in the partner state. All countries have signed for the implementation of the AMDD in 2015,

but the current state of implementation of the different member states vary and is not completed yet. [65]

4.3.4 *Eurasian Economic Commission*

The Eurasian Economic Comission (EEC) is a union of states. Part of this Union are: the Republic of Armenia, the Republic of Belarus, the Republic of Kazakhstan, the Kyrgyz Republic and the Russian Federation. The Commission started working in 2012 for ensuring the development of the Eurasian Economic Union and develop further integration.

In 2016 the EEC has published the Eurasian Medical Device Registration Rules, which shall help unifying the requirements of the different countries. This system is similar to the European CE marking system. The member countries now try to adapt to the required system, which will be fully effective in December 31st 2021. A practical approach to the system is hard though, since some elements of the new system are still unclear. Therefore the member states are currently performing registration according to their old systems. [66]

4.3.5 *International Medical Device Regulators Forum*

The International Medical Device Regulators Forum (IMDRF) is a voluntary group and was founded in 2011 to continue the work of the Global Harmonization Task Force (GHTF), which was founded in 1992. The GHTF aimed to enable a greater compliance of national device regulatory systems for a higher patient`s safety and to effectively protect clinical beneficial medical technologies around the world. The founding members of this organization were the EU, the USA, Canada, Australia and Japan between them the chairmanship was rotated. [67]

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. [68]

One topic the IMDRF worked on was the Medical Device Single Audit Program (MDSAP), which is very oriented on the ISO 13485:2016. Audits conducted by different regulatory authorities at the manufacturer's sites should be reduced by the recognition of one audit, performed by MDSAP certified company. This would make sense, since the audits are often redundant inspections, but result in different QMS audit reports. As a preventive action the MDSAP includes the unification by a clear evaluation system. Audits require a lot of preparation and take mostly more than one day, so also time effort would be minimalized. Finally, the communication between the regulatory authorities would be improved and manufacturers, which do not perform properly, would be identified more easily and it would be more difficult to slip through the system.

A test run was accomplished in 2017 conducted by Australia, Brazil, Canada, Japan and the USA. The EU and WHO were observing the progress. The result of the test run was, that all countries approve MDSAP audits, but with some exceptions. Canada is the only one, who exclusively accepts MDSAP Audits anymore for QMS certification. MDSAP audits are conducted by so called Auditing Companies, which must be certified accordingly.

To sum up the MDSAP test run, the manufacturers were reserved, since there are also disadvantages in correspondence with the program. The audit result is apparent to all member states, which could lead the national regulatory authorities to perform additional audits. Additionally, the list of requirements is longer, since it is the combined sum of the national requirements. Finally one major disadvantage would be, that the EU, being a big market, is not participating. [27]

4.3.6 *World Health Organization*

The World Health Organization (WHO) is a coordination authority of the United Nations and was founded on April 7th 1948. Currently there are 7000 people working in 150 different offices all over the world. The organization's principle is that everyone deserves the highest possible standard of health regardless of race, religion, political belief, economic standard or social condition. [69]

In 2001 the WHO provided the first framework by publishing *"A model regulatory program for medical devices: An international guideline"* to encourage member states to establish regulatory programs for medical products. The aim of this guideline was to enable the definition of internationally compatible regulations. [8]

In 2003 *"Medical device regulations. Global overview and guiding principle"* was published where the complexity of the medical device industry was described and issues related to regulations were identified. This guideline was aiming to provide information for member states which want to create or modify the regulatory system for medical products. [8]

4.4 Registration procedure of the e|1 Analyzer

The before mentioned data forms the knowledgebase for the creation of the registration procedure of the e|1 Analyzer (further on referred to as “e|1”), which is the first product to be placed on the market by the company EXIAS Medical, located in Graz, Austria. This product is intended for the measurement of electrolytes in either laboratories or POC testing environment. Lay persons are excluded from the determined user group.

The e|1 is developed, designed and produced with the support of a QMS which consists of more than 50 standard operating procedures and was certified in autumn 2018 according to the ISO 13485:2016 by the TÜV Süd.

Before placing the product on the target markets (Argentina, Brazil, China, Egypt, India, Indonesia, Mexico, Philippines and Vietnam), the EU conformity assessment procedure, resulting in the CE-marking of conformity will be completed. This procedure is depicted via the process flow chart in figure 6. The overall process of registration is depicted in figure 7. On the left-hand side inputs to each procedural step are depicted and the right-hand side shows outputs. These can be either documents or again independent procedures.

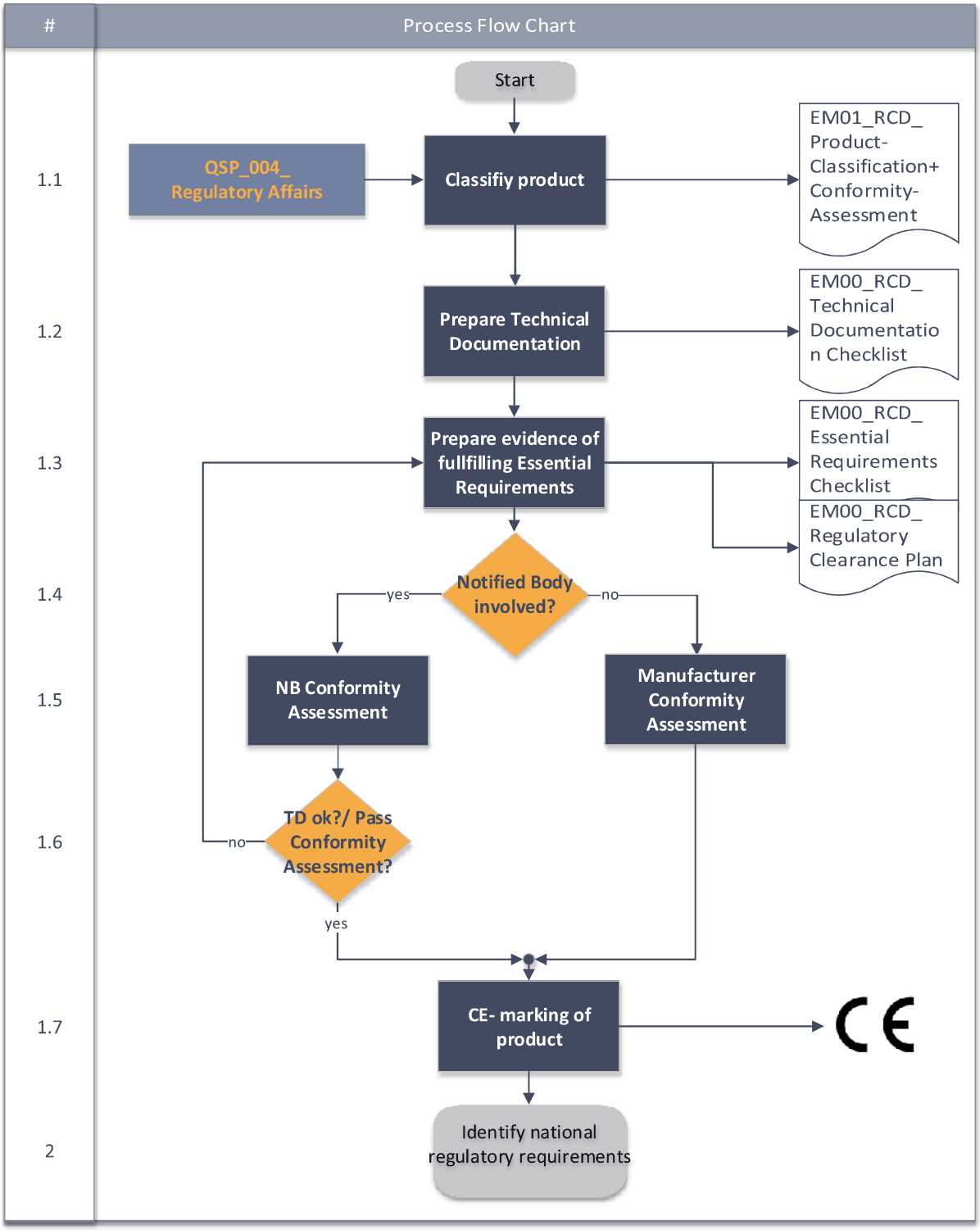


figure 6: Process flow chart of conformity assessment procedure of the EU

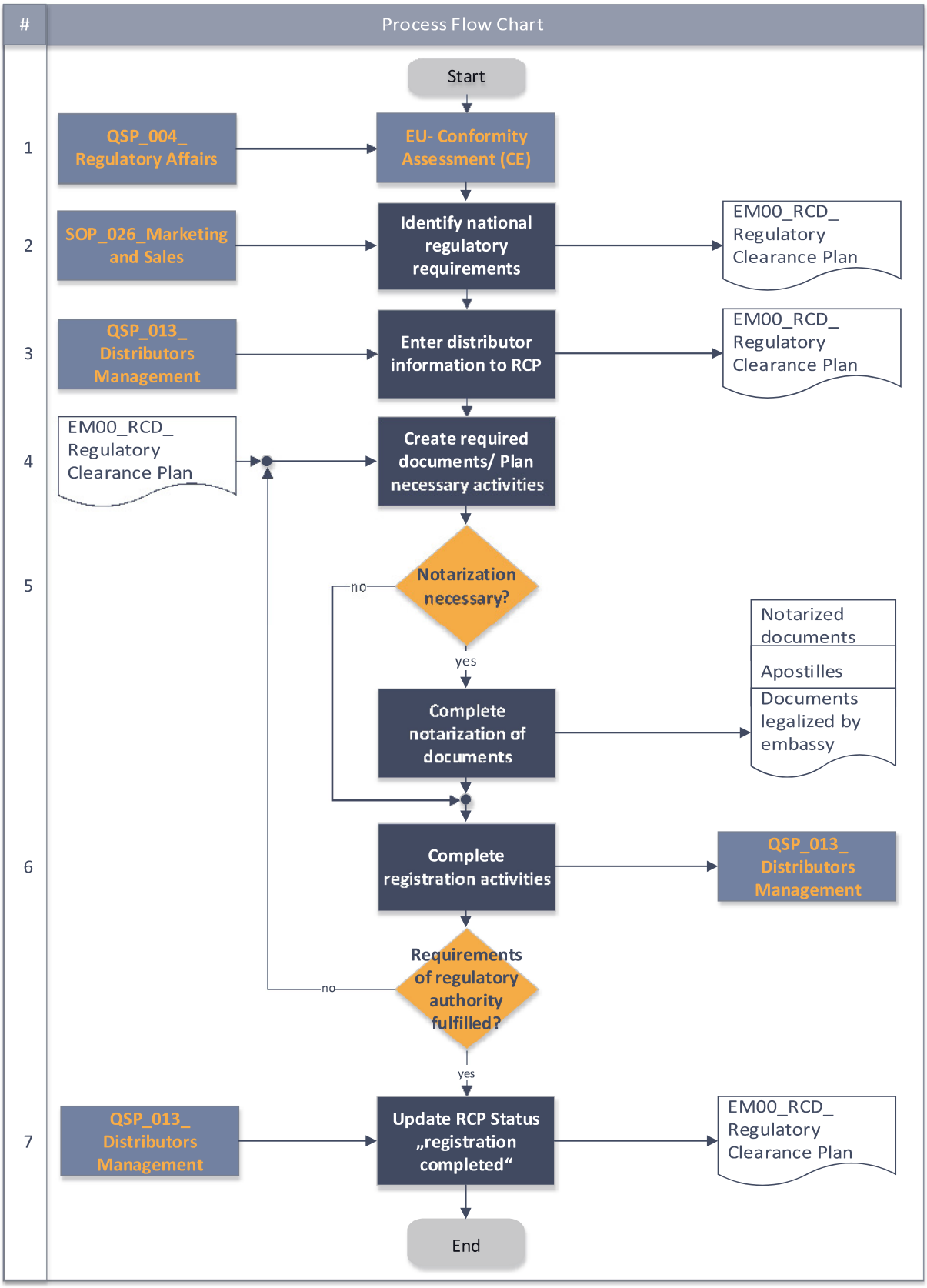


figure 7: Process flow chart of registration procedure

EXIAS Medical will perform the conformity assessment procedure of the product according to the IVDD. Nevertheless, it will cost much effort to convert to the new legislation, which must be complied with latest on the 26th of May 2022. Therefore, the SOP already includes the market placement requirements according to the IVDR.

Before deciding what kind of conformity assessment is possible for the product, it must be classified. Therefore the classification systems of the IVDD as well as the IVDR must be investigated.

As already mentioned in chapter 4.1, there are two lists described with IVDs, which inherit higher risk potential (see table 2):

List	Description
List A	– Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell, – Reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.
List B	– Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd, – Reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies, – Reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis, – Reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria,

List	Description
	– Reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia, – Reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B, – Reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA, – Reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21, – the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

table 2: Lists described in Annex II IVDD

Since the measurement of electrolytes is neither listed on List A, nor on List B, the e|1 can be classified as General IVD. Self-testing can be excluded as well, whereas it is intended to be used by laboratory- or clinical experts and not by lay persons in a home environment. [13]

The rules described in Annex VIII of the IVDR are listed in the following table 3:

Rule	Description
Rule 1	Devices intended to be used for the following purposes are classified as **class D**: – detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration;

Rule	Description
	– detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation; – determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management.
Rule 2	Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as **class C**, except when intended to determine any of the following markers: – ABO system [A (ABO1), B (ABO2), AB (ABO3)]; – Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]; – Kell system [Kel1 (K)]; – Kidd system [JK1 (Jka), JK2 (Jkb)]; – Duffy system [FY1 (Fya), FY2 (Fyb)]; in which case they are classified as **class D.**
Rule 3	Devices are classified as **class C** if they are intended: (a) for detecting the presence of, or exposure to, a sexually transmitted agent; (b) for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation; (c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring; (d) for pre-natal screening of women in order to determine their immune status towards transmissible agents; (e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient

Rule	Description
	management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (f) to be used as companion diagnostics; (g) to be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (h) to be used in screening, diagnosis, or staging of cancer; (i) for human genetic testing; (j) for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (k) for management of patients suffering from a life-threatening disease or condition; (l) for screening for congenital disorders in the embryo or foetus; (m)for screening for congenital disorders in new-born babies
Rule 4	(a) Devices intended for self-testing are classified as **class C**, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as **class B.** (b) Devices intended for near-patient testing are classified in their own right.
Rule 5	The following devices are classified as **class A**: (a) products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination; (b) instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures;

Rule	Description
	(c) specimen receptacles.
Rule 6	Devices not covered by the above-mentioned classification rules are classified as **class B**.
Rule 7	Devices which are controls without a quantitative or qualitative assigned value are classified as **class B**.

table 3: classification rules of the IVDR

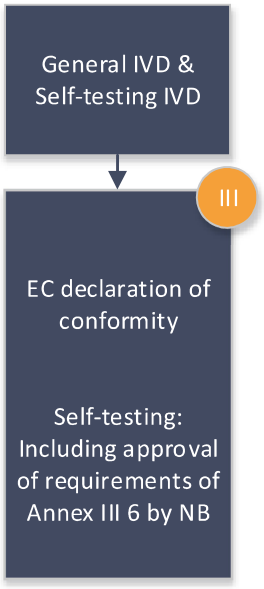
The e|1 results in the risk class B, since rule 6 of the 7 classification rules is applicable. This rule says that all devices not covered by rule 1-5, can be classified as class B.

An assignment to the group of self-testing or companion devices is not applicable, since the user is not a lay person but a health care professional and the e|1 is not essential for the use of a corresponding medicine. But the e|1 is a device for near-patient testing. The additional requirements for this product group must be considered. [3]

For each medical product a technical documentation (TD) must be created. Hence requirements are expressed in Annex III of the IVDD and Annex IX of the IVDR which are filled into the Technical Documentation Checklist. This list contains the paragraphs of the legislations, if they are applicable or not including a justification and the relevant records for the evidence of the requirements.

Since the technical documentation described in the IVDD is not very informative, the guidance document provided by the GHTF GHTF/SG1/N063:2011 with the title Summary Technical Documentation (STED) is also consulted. This guideline is far more comprehensive and the practical implementation is depicted clearer.
The requirements of the TD are described in Annex IX of the IVDR.

One requirement of the TD is the fulfilment of the Essential Requirements (IVDD Annex I) or rather of General Safety and Performance Requirements (IVDR Annex I). Both are listed in the Essential Requirements Checklist. The structure of this list is the same as of the Technical Documentation Checklist.



After having determined the risk class of the device, the conformity assessment procedure can be chosen. The manufacturer of a General IVD does not require a notified body to evaluate the conformity assessment. A self-declaration of conformity can be performed (see figure 8).

figure 8: EC declaration of conformity acc to IVDD for General IVDs

As soon, as the e|1 shall be placed on the market according to the IVDR, a notified body will be necessary for the conformity assessment procedure since that will be obligatory for class B products. Then the conformity assessment procedure according to Annex IX will be applicable for the e|1 based on a QMS and the assessment of the technical documentation. Section 5.1 of this Annex must also be considered since the e|1 is meant for near-patient testing (see figure 9).

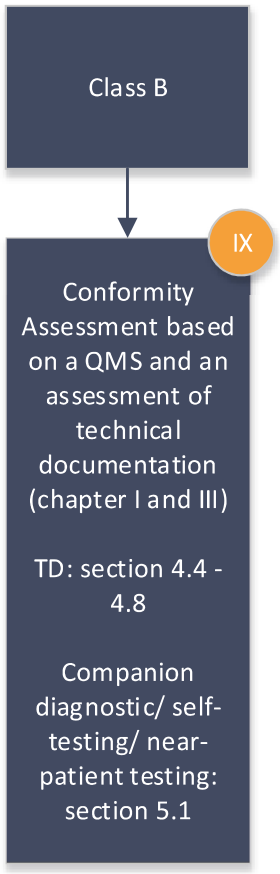


figure 9: Conformity assessment based on QMS and assessment of TD acc. IVDR for class B IVDs

After concluding the EC declaration of conformity according to Annex III including providing the evidences requested by the Essential Requirements- and Technical Documentation Checklists, the CE-marking of conformity will be affixed on the e|1 as required in Annex X of the directive.

As soon as a notified body is involved in the conformity assessment procedure, the notified body will check the QMS as well as the TD and will evaluate the procedure. Since the QMS of EXIAS Medical is already ISO 13485:2016 certified, an additional inspection will not be necessary.

After a positive conformity assessment procedure, the CE-marking of conformity will be affixed on the e|1 as required in Annex V of the regulation. Here the number of the notified body follows the CE-marking of conformity.

After the CE-marking, the requirements of the designated markets will be filled into the RCP. Since EXIAS Medical will distribute the e|1 via a network of distributors all over the world, those will be responsible for the national registration. Therefore, they will send information about the registration requirements, which will be filled into the RCP. This plan consists of generally three sheets, which collect registration relevant data. The sheet “Regulatory Clearance Plan” contains specific document required by different countries, whereas the sheet “Registration Information” lists all relevant data about classification of product, national regulatory authorities, timelines of registration and reregistration, the need for a FSC or the legislation status of documents. The sheet “IFU&Label Requirements” collects data about language requirements of the product.

Administrational documents, which are often required for the registration are Letters of Authorisation (LoA), the Free Sales Certificate (FSC), signed Distributor contracts and Power of Attorneys (PoA). For the LoA and the PoA, templates are created. The FSC is a document, which is created by the BASG (“Bundesamt für Sicherheit und Gesundheitswesen“), which represents the Austrian regulatory authority. This document can be requested, after the CE-marking of conformity is affixed. The FSC approves that the corresponding product is placed on the Austrian market thus the market of the European Union lawfully. It can be requested for more than one country at a time, so a collected request is reasonable for the avoidance of further costs.

Generally, the FSC will be valid for two years after it has been issued by the BASG, if no significant changes to the product have been made. [70]

After the determination of the requirements applicable records will be created, or registration activities will be planned and conducted. All relevant data will be sent to the distributor either legalized or not, dependent on what the distributor requires, resulting in a registration notice of the distributor.
After the registration is completed, reregistration activities must be inquired and filled into the RCP. These reregistration activities must be planned early enough, to prevent financial damage by losing market approval in a country.

The SOP drafted for EXIAS Medical is attached in Annex I of the thesis and Annex II contains the Regulatory Clearance Plan.

5 Discussion

5.1 Classification systems

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 defined product groups which are already assigned to a risk class. By the assignment to a product group the risk class can be determined.

Comparing the GHTF classification of MDs with the directive itself, it can be seen, that the GHTF uses one rule less (17 instead of 18) than the directive. The directive´s rule number 18 describes the classification for blood bags which is integrated into rule 2 of the GHTF guideline. So there is no content related difference. [12, 9].

The MDR added 4 rules for the device classification and used the approach of the GHTF by integrating the classification of blood bags into rule number 2 as well as AIMDs. The influence of the GHTF on the EU regulation is unambiguous. Other than adding more specific definitions and more defined wording, the extension of rules 8, 9 and 10 and the definition of rule 11, 19, 20, 21 and 22 has been adapted.
Rule 11 describes software as a medical product and tries to classify software by evaluating the impact on patients after a decision is made using that software.
Rule 19 describes nanomaterials and rule 20 covers products intended to administer medical products by inhalation. Rule 21 describes products intended to be introduced into or to be absorbed on the body and rule 22 covers active therapeutic devices with an integrated diagnostic function. [2]

Comparing the classification of the GHTF guideline and IVDD no accordance can be found due to the complete different approach of the classification. But a comparison of the rules of the GHTF guideline and the rules defined in the IVDR, reveals clear content related compliance. [3, 13, 14]

The influence of the GHTF guidelines on the EU regulations makes sense considering that the EU was a founding member of the GHTF and therefore had a say in the different study groups. [67]

Comparing a rule-based classification system of the EU and a group-based classification systems like in the USA, it can be seen, that rule based classification systems do not need as many maintenance activities, compared to group-based classification systems. If a product cannot be assigned to an existing product group for the registration of the product in the USA, it will be assigned automatically to the highest risk class. This means a higher effort for the manufacturer as well as the regulatory authority and results in higher registration costs. This approach is a market barrier, but safer for patients, since there is no possibility of slipping through the system, like it is possible in a rule-based classification system. But from time to time an update of the rules must be done too to maintain their effectiveness.

The Roszdravnadzor has been criticized by members of the medical device industry, that their classification system of medical devices would not be practical and the classification by the manufacturer would be more appropriate compared to experts in the field of the biomedical engineering sector. Therefore the Roszdravnadzor has released a resolution in 2017 allowing manufacturers of MDs to discuss specific aspects and requirements of the registration procedure with the national regulatory authority. A close collaboration between regulatory authorities and manufacturers is supporting an efficient procedure of registration. [20]

No matter what kind of classification system is used, either rule-based or group-based, a risk-based approach for product registration is reasonable and enables high controls, where it is really needed, e.g. for products which could harm patients, users or have negative impacts on public health. Nevertheless a trend can be identified in countries which are just starting to define classification systems which are heading towards the four-tier based classification system.

5.2 Regulatory requirements worldwide

Countries, which do not have a regulatory system for medical products like some nations in Africa, must focus on defining a regulatory landscape. Regulatory bodies must be established for the control of medical products throughout their life cycle. For future development of the regulatory landscape, a bridge must be built in Africa between the experts in the laboratories, that have knowledge about medical products and experts of the regulatory systems. Laboratories must be supplied with proper equipment to perform clinical studies, for both pre- and post-market controls.

The finalization of regulations for IVDs for fast diagnosis of infectious diseases like HIV/AIDS, tuberculosis or malaria will have high priority, which is understandable in the light of the current health needs in this developing country. To accelerate the access to affordable and safe products, a harmonization of the requirements is to be accomplished, which shall be promoted by the PAHWP. [7]

Economic burdens on manufacturers in developing countries must be considered. Harmonization of the legislations is one way to support the manufacturer. Another way could be the so called Open source medical devices (OSMD). The design of an OSMD means sharing ideas, concepts and design files. Source Codes, test results and prototypes are accessible for many experts in the field and also in the regulatory landscapes. This means more input for the design of the devices, as well as for the creation of regulatory documents. This intrinsic revision process results in safer and more effective medical devices and reduces costs. A final registration procedure must still be completed including the verification of the quality of the product. Nevertheless, due to the share of knowledge, manufacturers in developing countries are supported sustainably in their design procedure including the registration of the product. [6]

Highly sophisticated regulatory authorities should continue working on their procedure`s efficiency, like for example the US-american FDA. The FDA is updating its registration procedures constantly. New guidance papers are released, trying to help manufacturers with a practical implementation of the registration procedures. Additionally the national authority also wants to ease the registration procedure 510(k). An electronic submission of the documents shall be obligatory (“e submitter”).

Processing time shall be shortened from 90 to 60 days and an interactive review for improvements and open questions shall be possible, also aimed to reducing processing time. This option is currently only for approximately 40 product codes available though.

Not only the 510(k) procedure will be more efficient, the Premarket Approvals will be accelerated by reducing printed documents and making digital communication possible also. Again the interaction between manufacturers and the national regulatory authority will be faster. In summary the FDA tries to focus its strict approval on high risk products. [71]

Regarding its QMS, the FDA has announced, that there may be a change in the process 21 CFR 820 including the harmonization with the ISO 13485. The ISO refuses this harmonization though, due to the non-profitable publication of quality standards on the homepage of the FDA. ISO, being a private institution, charges for their standards. [71, 72]

A harmonization would be reasonable removing regulatory hurdles and expediting access to high quality products. Especially considering the fact that the FDA has a saying in shaping the content of the ISO 13485 having representatives as part of the working group. The content is to 95% alike and the handling of the other 5% must be identified and a plan on how to address those must be created before further negotiations can be attempted to. It is important that a solution is found for that issue, since the victims of this power struggle are the manufacturers. [72, 73, 35]

As soon as new legislations are installed like in the EU, the regulatory authority should provide guidance papers. Clearly defined guidance papers help the manufacturer to implement such systems and the regulatory authority to understand the obstacles manufacturers are confronted with. New legal bases tend to be more extensive and more precise after each update. Realistic time frames and transition periods help manufacturers as well as regulatory authorities to adapt to the new system.

The new regulatory landscape defined by the 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.

One negative aspect of the new regulations would be the “common specifications” (CS), which are mentioned in the legal act. These specifications have not been defined yet, leaving a gap in the regulations. As soon as they are definitely effective, the manufacturer must comply also with these common specifications. Dependent on the extent of these documents, the manufacturer must then react quickly and invest resources to fulfil these still unknown requirements. [11]

Another disadvantage for innovation in the medical devices sector of the EU would result from the lack of specialists required by the regulations. The closing of notified bodies and the high requirements for possible auditors of notified bodies have major impact on the efficiency of the registration procedure. Without staff a notified body will require more time completing conformity assessment procedures. What´s more: the new regulations dictate that an increased number of manufacturers of medical products needs a notified body involved in their conformity assessment procedures. Where according to the directives many MDs and IVDs are classified as class I devices or General IVDs, which allows a self-declaration of the manufacturer, skipping involvement of a notified body in the conformity assessment procedure, the regulations changes that. According to the regulations´ classification systems, many products are upgraded relating to their risk class, which results in the obligation for a notified body included in the conformity assessment procedure, where there was none needed before.

So not only have many notified bodies of the EU been closed, also more manufacturers will require their services for the conformity assessment procedure. The transition period for MD manufacturers will expire in May 2020 and the first notified bodies will be notified to perform conformity assessment procedure according to the regulations at the earliest in the second half of 2019. [11]

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.

5.3 Harmonization groups

A major advantage of harmonization groups is the collaboration of regulatory authorities and manufacturers in study groups. They manage to build that important bridge between legislation and practical implementation. The input of manufacturers is one of the reasons, why the guidelines of harmonization groups are more practically designed. Their influence on regulatory requirements can be displayed clearly in the latest regulatory update of the EU. Not only the classification system of IVDs of the IVDR has been adapted to the guideline of the GHTF for IVD classification, but also the requirements for technical documentations are similar, at some points even identical, to the guideline of the STED.

The regulations issued by the European Commission and the European Parliament for medical products have been harmonized since the 1990's by issuing one set of regulations for all member states. Market placement of the product in one member state enables market placement in other member states as well. But individual national requirements are still to be considered by manufacturers like language requirements for the IFU or administrative register entries.

ASEAN countries agreed on one medical device directive, that shall be implemented by all member states. But this process is not completed yet. Nevertheless in the upcomming years broader harmonization of national requirement in Southeast Asia is to be expected.

Harmonization group's member countries, which have fewer financial resources than other member state, are disadvantaged in that kind of system though. Regulatory requirements are always coupled with financial effort. If the system is highly sophisticated and accordingly expensive, local manufacturers cannot bear the financial load. A support system is requested to avoid the discrimination of less developed countries in combination with this kind of harmonization.

Another possible approach for the reduction of trading barriers would be the recognition of state of the art registration procedures. The ISO 13485 is acknowledged by many countries as a QMS evidence. Also the MDSAP serves as a good example.

This program is a promising approach of reliving manufacturers for financial and time effort for QMS audits. Audits are important for controlling manufacturers, whose job it is to be profit oriented. An inspection of a third party can rearrange the perspective and prevent harm to patients, users or society. Since audits are conducted by a number of regulatory authorities, harmonizing these activities enables manufacturers to focus resources on developing high quality products and improving production procedures. [61, 74]

Countries, which have not implemented a regulatory framework yet, should orient themselves on existing guidelines like the IMDRF and the WHO and, if necessary, adapt them to its current social, political and health state. A harmonization with neighbour states would be the beginning for reducing trade barriers.

Globally there is no extensive harmonization of medical product regulatory requirements yet. One challenge of harmonization is the different health standards and economic possibilities of the countries. Still in the last couple of years harmonization activities have increased especially in developing countries. These activities must be supported by industrial states since they also benefit from this development.

Another threat of harmonization is the growing interest on individual legislations. The trend goes back to the individuality of countries as well as regulations, which can be seen by the latest Brexit negotiations. The EU managed the harmonization of requirements for all of its member states. The population of Great Britain has voted for the exit of the EU in June 26th 2016, which results also in the exit of regulations described by the EU. The contract for the Brexit is now under negotiation, but the deadline for this event is set for March 29th 2019. Not only manufacturers in Great Britain will be affected by the arousing changes, also manufacturers which have chosen a notified body in Great Britain will be disadvantaged. The British Standard Institution (BSI) is one of the biggest notified bodies especially manufacturers of high-risk medical devices choose in the EU. The BSI has now started to move its formal head quarter to the Netherlands to provide further services to its customers. The final impact of the Brexit on the medical device industry is to be expected. [75, 76]

5.4 Registration procedure of the e|1 Analyzer

For some countries a CE-marking of conformity is not required, what is a sign of low health standards. The governments of these countries do not have the resources to ensure the safety of its population and to assure medical product quality. Still, EXIAS Medical has decided, that the conformity assessment according to the EU must be conducted to ensure the product quality. Not only the reputation of the company would be at stake but far more importantly the health of patients and users.

The final procedure represents a general description which can also be expanded to other IVDs, which are planned to be placed on the market by the company. A formation of possible country groups, where the same registration requirements are demanded, was not possible except for EU member states. But even there national variations must be considered. Still, the Regulatory Clearance Plan creates an overview of the different national requirements and helps to control registration activities.

The decision to place the product on the market first according to the directive and not the regulation was made not only because there are no notified bodies in the EU available yet for such activities, but because the conformity assessment procedure according to the directive is simpler for the e|1.

To assure product quality, EXIAS Medical has been ISO 13485:2016 certified. This QMS certification is recommended to every manufacturer. Not only because it is often requested by regulatory authorities but the effort of establishing a functional QMS does not make much difference to the effort of certifying the QMS by external auditors. Further on, the evaluation of the QMS by an external party always gives new perspectives and recommendations for improvement, which are very important especially for quality managers who may already have become blind to shortcomings in company procedures.

6 Conclusion

Access to affordable high quality medical products results in good health state of the population. This is only possible by establishing regulatory authorities, which define regulations and perform pre- and post-market controls and registration requirements. Manufacturers must provide proper evidence for the fulfilment of these requirements and should be supported by regulatory authorities during the registration procedure with guidelines as well as harmonization activities.

An efficient registration of medical products must be enforced by both the regulatory authority as well as the manufacturer. A dynamic regulatory system for medical products with few significant requirements, low registration costs and fast market availability with the focus on the patient`s safety and high-quality products on the market should be the goal. Harmonization of these requirements is encouraging this goal for access to high quality products which are affordable. But the diversity of social systems, political stability and economic situations complicates this harmonization goals. Developing countries need support for the creation of joint regulations and for the development of a solid health care system, which includes controlling of medical products. [7]

Still harmonization of regulatory requirements can be identified in the EU, where since the 1990’s medical device regulations have been standardized. Also in Southeast Asia the agreement on the ASEAN medical device directive will ease registration procedures there in the next couple of years. Due to the current state of uncompleted harmonization and therefore national variability in regulatory requirements, a registration procedure, which includes the formation of country groups where the same registration requirements are applicable is not possible except for member states of the EU.

A confrontation with national regulatory requirements is necessary. But by complying with the EU conformity assessment procedure and thus a good technical documentation and the fulfilment of general safety and performance requirements technical records required by other regulatory authorities can be covered. The ISO

13485 certification is advised for any manufacture not only because it is requested for registration in some countries, but also because of the benefit for the company and its QMS. Nevertheless the confrontation with national regulatory requirements is still necessary to assure an efficient procedure of registration.

7 Literature

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Doc Type	Annex I Standard Operating Procedure
Title	EM00_SOP_025_Product Registration
Project	EM00
Keywords	Registration, Regulatory Clearence, CE marking of conformity
Description	Guideline for the registration of EXIAS Medical productson the global market.

	Name	Date	Signature
Author	Magdalena Kedwani		
Review	Gerald Nauschnegg		
Review	Vincent Beuchon		
Approval	Udo Klinger		

Change history

Vers	Editor	Date	Change Description
01	Magdalena Kedwani	DRAFT	Initial content

Table of Contents

1 Purpose

This procedure is intended to control the registration of products produced and /or placed on the market by EXIAS Medical.

2 Scope

The scope of this document is to define an efficient procedure of registration of EXIAS Medical's products (IVDs) to save time and costs.

3 Terms and Definitions

Term	Definition
Apostille	Legislation of a document for countries which agreed on the "Haager Übereinkommen zur Befreiung ausländischer öffentlicher Urkunden von Beglaubigungen"
CE- marking of conformity	Marking by which a manufacturer indicates that a device is in conformity with the applicable requirements set out in the regulation/directive and other Union harmonization legislation (see IVDR Article 2 (35))
Companion diagnostics	A device which is essential for the safety and effective use of a corresponding medical product/ medicine.
End customer	Laboratory, hospital, health institution,
EU	European Union
General IVD	All devices which are neither described on List A, List B or for self-testing
GHTF	Global Harmonization Task Force on Medical Devices, voluntary group to encourage convergence in regulatory practices
IFU	Instructions for use
IMDRF	International Medical Device Regulators Forum, build on foundational work of GHTF and aims to accelerate international medical device regulatory harmonization and convergence
IVD	In vitro diagnostic medical device
IVDD	Directive on in vitro diagnostic medical devices (EU)
IVD for near-patient testing	any device that is not intended for self-testing but is intended to perform testing outside a laboratory environment, generally near to, or at the side of, the patient by a health professional; (see IVDR Article 2 (6))
IVD for self-testing	any device intended by the manufacturer to be used by lay persons, including devices used for testing services offered to lay persons (see IVDR Article 2 (5))
IVDR	Regulation on in vitro diagnostic medical devices (EU)
NB	Notified Body
Placing on the market	The first making available of a device, other than a device for performance study, on the Union market
STED	Summary Technical Documentation (GHTF/SG1/N063:2011) Guidance for creating the technical documentation according to the IVDD published by the former GHTF (now IMDRF)
TD	Technical documentation

4 Responsibilities

Role	Task / responsibility
Regulatory Compliance Manager	Responsible for the establishment of the procedure within EXIAS Medical.
Process Owner	Responsible for the registration of EXIAS Medical products, for overseeing the procedure including notarization activities, for initiating registration actions, creating of regulatory compliance documentation
Sales Manager	Identification of possible economic markets to launch the product in, communication with distributor
Distributor	Responsible for the registration in the respective market and handling of the communication with national regulatory authorities
Top Management	Provides relevant resources, decides on which markets the product is launched in, organizes notary, checks documents before they are sent to the distributor
Postal Service Responsible	Handles postal traffic of notarized documents
Notified Body	Involved in the conformity assessment procedure except for General IVDs or Class A IVDs

5 Interaction of procedures

This procedure interacts with the following other procedures.

Process	Input	Output
QSP_004_Regulatory Affairs	Identification of effective regulations or directives	
QSP_013_Distributors Management	Requirements for the product registration in the respective country gathered by the distributor Certificate for registration in different countries	Necessary documents
SOP_026_Marketing and Sales	Identifies markets the product shall be registered on	
SOP_34_Preparation of Project-/Product documents	Instructions for the creation of product documents.	

6 Description / Procedure

The following procedure is separated into two parts. First there is the EU- Conformity Assessment resulting in the CE marking of conformity, afterwards the product can be registered outside of the European market.

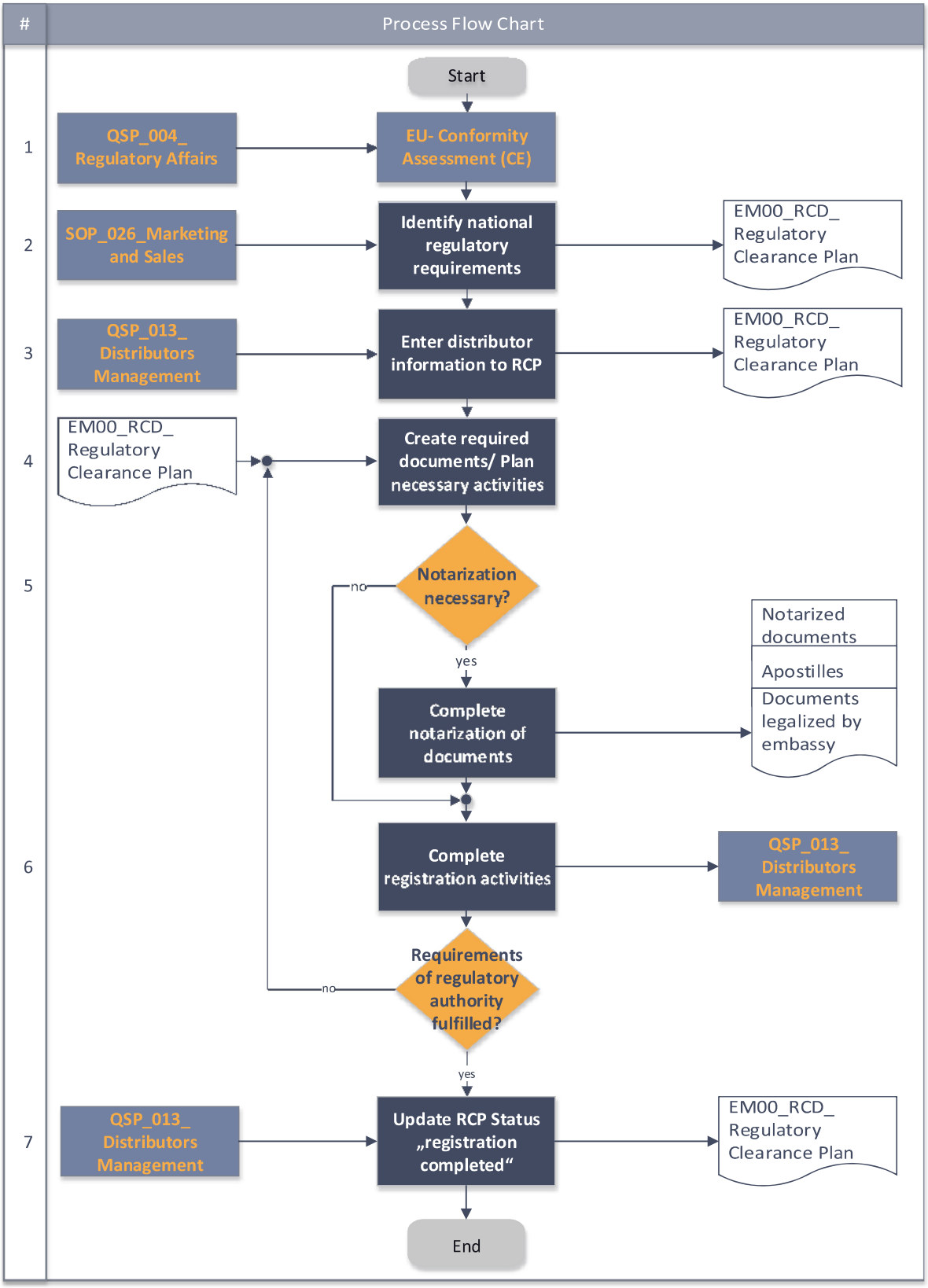

Figure 1: Process Flow chart of the product´s registration

6.1 #1: EU- Conformity Assessment (CE- marking of conformity)

Before registering the product on markets outside of the European Union, the product shall gain the CE marking of conformity. Therefore, the product must be in conformity with the applicable legislation of the European Union which is identified in the procedure of Regulatory Affairs (see [1]).

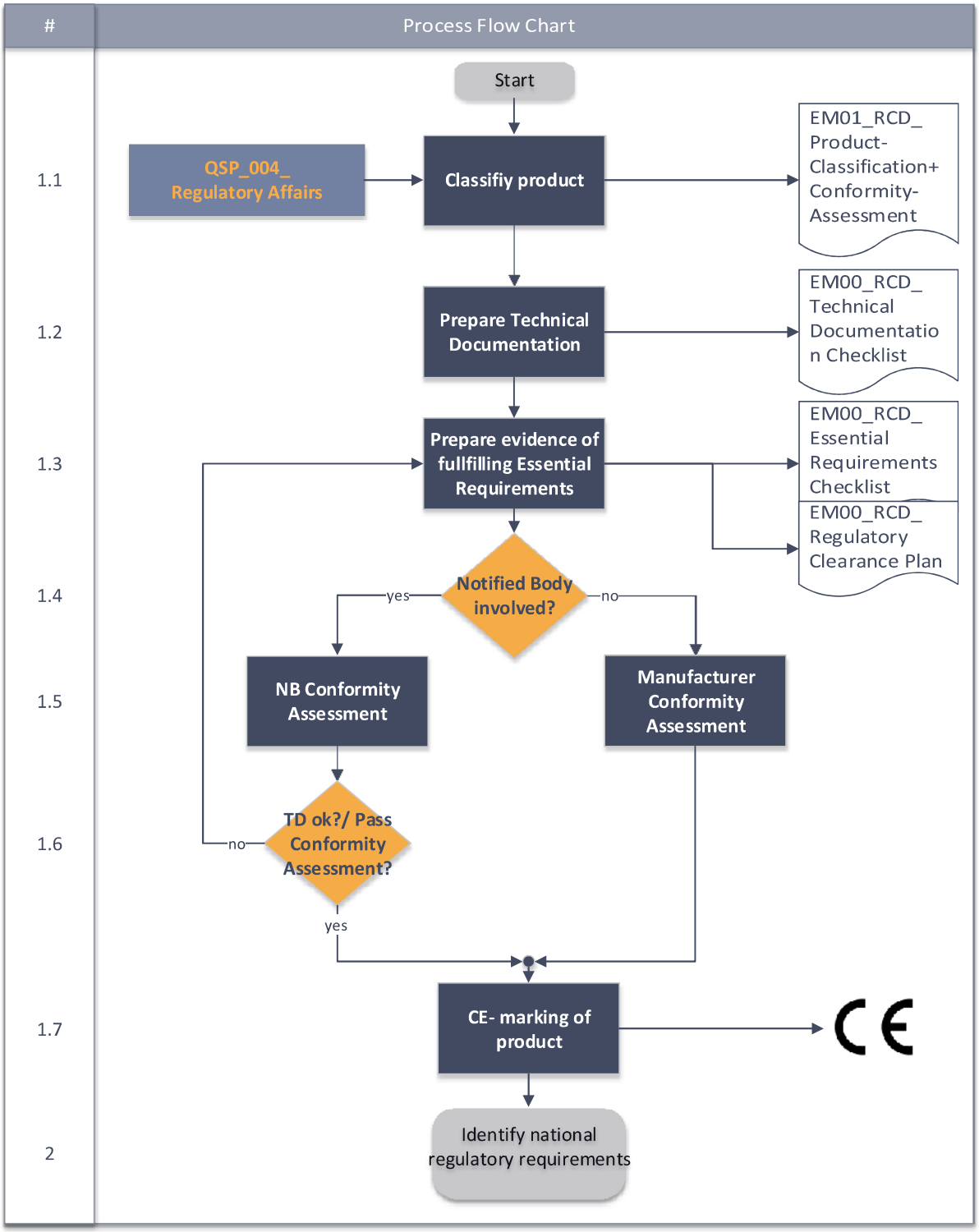

Figure 2: Process Flow Chart of the product´s registration within the EU

6.1.1 #1.1 Classify product

The classification of the product shall be conducted by using the applicable rules described in the either the IVDD or the IVDR. Depending on the classification of the product, the conformity assessment procedures vary. The result of this process step is the documented classification of the product (see {3})

6.1.1.1 Classification acc. to the IVDD

The IVDD (see {1}) classifies the product by defining List A and List B devices in Annex II (see Table 1), where List A devices represent high risk products and List B devices moderate risk devices.

List	Description
List A	- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: ABO system, rhesus (C, c, D, E, e) anti-Kell, - Reagents and reagent products, including related calibrators and control materials, for the detection, confirmation and quantification in human specimens of markers of HIV infection (HIV 1 and 2), HTLV I and II, and hepatitis B, C and D.
List B	- Reagents and reagent products, including related calibrators and control materials, for determining the following blood groups: anti-Duffy and anti-Kidd, - Reagents and reagent products, including related calibrators and control materials, for determining irregular anti-erythrocytic antibodies, - Reagents and reagent products, including related calibrators and control materials, for the detection and quantification in human samples of the following congenital infections: rubella, toxoplasmosis, - Reagents and reagent products, including related calibrators and control materials, for diagnosing the following hereditary disease: phenylketonuria, - Reagents and reagent products, including related calibrators and control materials, for determining the following human infections: cytomegalovirus, chlamydia, - Reagents and reagent products, including related calibrators and control materials, for determining the following HLA tissue groups: DR, A, B, - Reagents and reagent products, including related calibrators and control materials, for determining the following tumoral marker: PSA, - Reagents and reagent products, including related calibrators, control materials and software, designed specifically for evaluating the risk of trisomy 21, - the following device for self-diagnosis, including its related calibrators and control materials: device for the measurement of blood sugar.

Table 1: IVDD Annex II

Products for self-testing which are not part of neither List A nor List B must fulfill additional requirements which are described in Annex III (6).

All other in vitro diagnostic medical devices which are not intended for self-testing or part of the before said list are so called General IVDs.

Since the products of EXIAS Medical (e|1 Analyzer, capillaries) are not part of neither of the lists, the products can be classified as **General IVDs.**

6.1.1.2 Classification acc. to the IVDR

The IVDR (see {2}) classifies the product by seven rules which are described in Annex VIII (see Table 2).

Rule	Description
Rule 1	Devices intended to be used for the following purposes are classified as **class D**: - detection of the presence of, or exposure to, a transmissible agent in blood, blood components, cells, tissues or organs, or in any of their derivatives, in order to assess their suitability for transfusion, transplantation or cell administration; - detection of the presence of, or exposure to, a transmissible agent that causes a life-threatening disease with a high or suspected high risk of propagation; - determining the infectious load of a life-threatening disease where monitoring is critical in the process of patient management.
Rule 2	Devices intended to be used for blood grouping, or tissue typing to ensure the immunological compatibility of blood, blood components, cells, tissue or organs that are intended for transfusion or transplantation or cell administration, are classified as **class C,** except when intended to determine any of the following markers: - ABO system [A (ABO1), B (ABO2), AB (ABO3)]; - Rhesus system [RH1 (D), RHW1, RH2 (C), RH3 (E), RH4 (c), RH5 (e)]; - Kell system [Kel1 (K)]; - Kidd system [JK1 (Jka), JK2 (Jkb)]; - Duffy system [FY1 (Fya), FY2 (Fyb)]; in which case they are classified as **class D**.
Rule 3	Devices are classified as **class C** if they are intended: (a) for detecting the presence of, or exposure to, a sexually transmitted agent; (b) for detecting the presence in cerebrospinal fluid or blood of an infectious agent without a high or suspected high risk of propagation; (c) for detecting the presence of an infectious agent, if there is a significant risk that an erroneous result would cause death or severe disability to the individual, foetus or embryo being tested, or to the individual's offspring; (d) for pre-natal screening of women in order to determine their immune status towards transmissible agents; (e) for determining infective disease status or immune status, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (f) to be used as companion diagnostics; (g) to be used for disease staging, where there is a risk that an erroneous result would lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (h) to be used in screening, diagnosis, or staging of cancer; (i) for human genetic testing; (j) for monitoring of levels of medicinal products, substances or biological components, when there is a risk that an erroneous result will lead to a patient management decision resulting in a life-threatening situation for the patient or for the patient's offspring; (k) for management of patients suffering from a life-threatening disease or condition; (l) for screening for congenital disorders in the embryo or foetus; (m) for screening for congenital disorders in new-born babies

Rule	Description
Rule 4	(a) Devices intended for self-testing are classified as **class C**, except for devices for the detection of pregnancy, for fertility testing and for determining cholesterol level, and devices for the detection of glucose, erythrocytes, leucocytes and bacteria in urine, which are classified as **class B**. (b) Devices intended for near-patient testing are classified in their own right.
Rule 5	The following devices are classified as **class A**: (a) products for general laboratory use, accessories which possess no critical characteristics, buffer solutions, washing solutions, and general culture media and histological stains, intended by the manufacturer to make them suitable for in vitro diagnostic procedures relating to a specific examination; (b) instruments intended by the manufacturer specifically to be used for in vitro diagnostic procedures; (c) specimen receptacles.
Rule 6	Devices not covered by the above-mentioned classification rules are classified as **class B**.
Rule 7	Devices which are controls without a quantitative or qualitative assigned value are classified as **class B**.

Table 2: IVDR Annex VIII

For the e|1 Analyzer Rule 6 is applicable, resulting in the risk **class B** since the intended use is not described by any of the Rules 1 – 5.

Since capillaries are specimen receptacles, Rule 5 is applicable, which results in risk **class A.**
For the documentation of the risk classification of the capillary tubes the company, they are purchased from, is responsible.

6.1.2 #1.3: Prepare Technical Documentation

The technical documentation is described in the IVDD in Annex III. The requirements of the technical documentation of the directive is listed in the Technical Documentation Checklist (see [3]) in the sheet "IVDD". The requirements of the IVDD are not sustainable though. Therefor the guideline of the former GHTF, now IMDRF, is screened. The requirements described in this guidance GHTF/SG1/N063:2011 with the Title Summary Technical Documentation (STED) are listed within the TD-Checklist sheet "IVDR-STED".

By filtering the TD-checklist for the risk classes, the different applicable sections can be found.

In 2022, when the IVDR will be fully effective, the requirements for the technical documentation described in Annex II and III must be met. Therefor the requirements of the IVDR are also part of the Checklist. Any additional necessary records must be created for the conformity assessment according to the IVDR.

6.1.3 #1.2: Prepare evidence of fulfilling Essential Requirements

One requirement of the technical documentation is the evidence of fulfilling the Essential Requirements. These Essential Requirements which correspond to the General Safety and Performance Requirements within the IVDR, are traced in an individual checklist, the the Essential Requirements Checklist (see [2]).

This list contains the requirements described in the directive and the corresponding record including, if the requirement is applicable for the product. If this is not the case, a justification must be described in this list.

The IVDR changes the definition of the Essential Requirements to General Safety and Performance Requirements. Those are also drafted in this list. Not later than the 26th of May 2022 all records for General Safety and Performance Requirements must be completed. Additional records must be created for the conformity assessment procedure according to the IVDR.

The Essential Requirements Checklist demands an instruction for use (IFU) for each device. This IFU must comply with national language requirements depending on the country the product shall be used in. These language requirements are collected within the Regulatory Clearance Plan (see[4]). This document traces national regulatory requirements worldwide.

6.1.4 #1.4: Notified Body involved?

Dependend on the classification of the device, a Notified Body must be involved in the conformity assessment procedure.

Until the 26th of May 2022 manufacturers of General IVDs do not need a Notified Body for the conformity assessment according to the IVDD. All other IVD manufacturers (manufacturers of products of List A, List B and for self-testing products) must involve a Notified Body in their conformity assessment procedure.

Since the products of EXIAS Medical are General IVDs, no Notified Body will be involved in the conformity assessment procedure. By creating the evidence for the requirements of the TD-Checklist and the Essential Requirements Checklist, the fulfillment of the requirements of the IVDD is confirmed.

As soon as the IVDR is effective, IVDs must be classified according to the rules already described in chapter 6.1.1.2.. Products of class A do not need a Notified Body involved in the conformity assessment procedure. All other products (class B-D) require the participation of a Notified Body, what is applicable for the products placed on the market by EXIAS Medical (except for the capillary tubes).

6.1.5 #1.5: Conformity Assessment

The IVDD describes the following conformity assessment procedures (see Figure 3). The numbers in the orange circles are the numbers of the applicable Annexes.

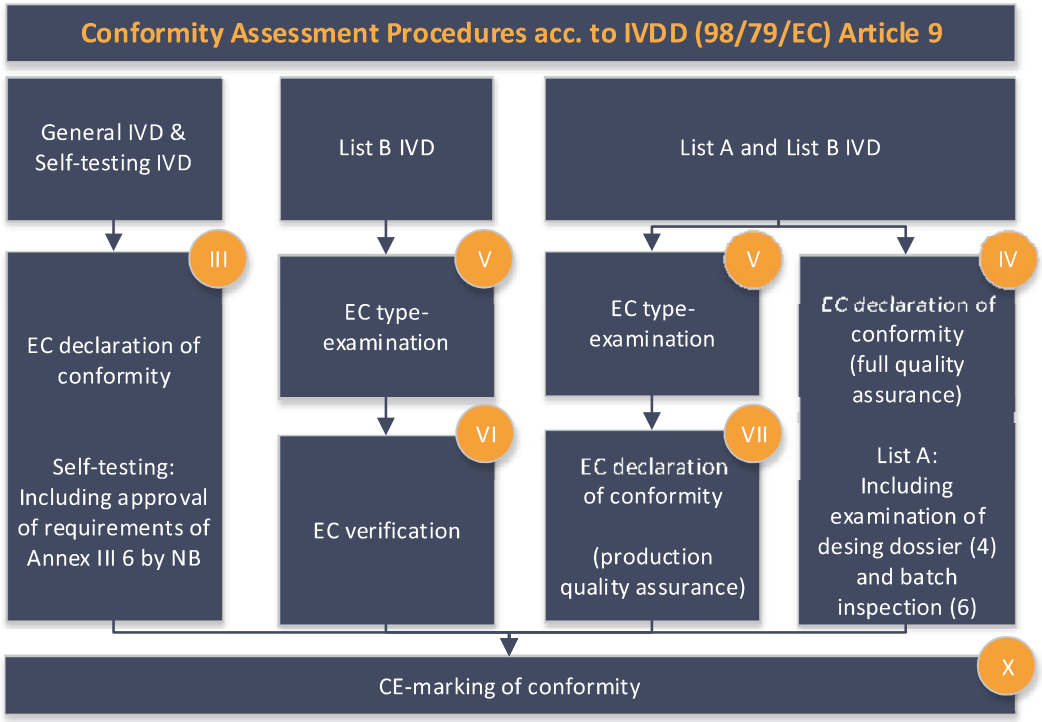

Figure 3: Conformity assessment procedures IVDD

The IVDR describes the following conformity assessment procedures dependent of the risk classification (see Figure 4).

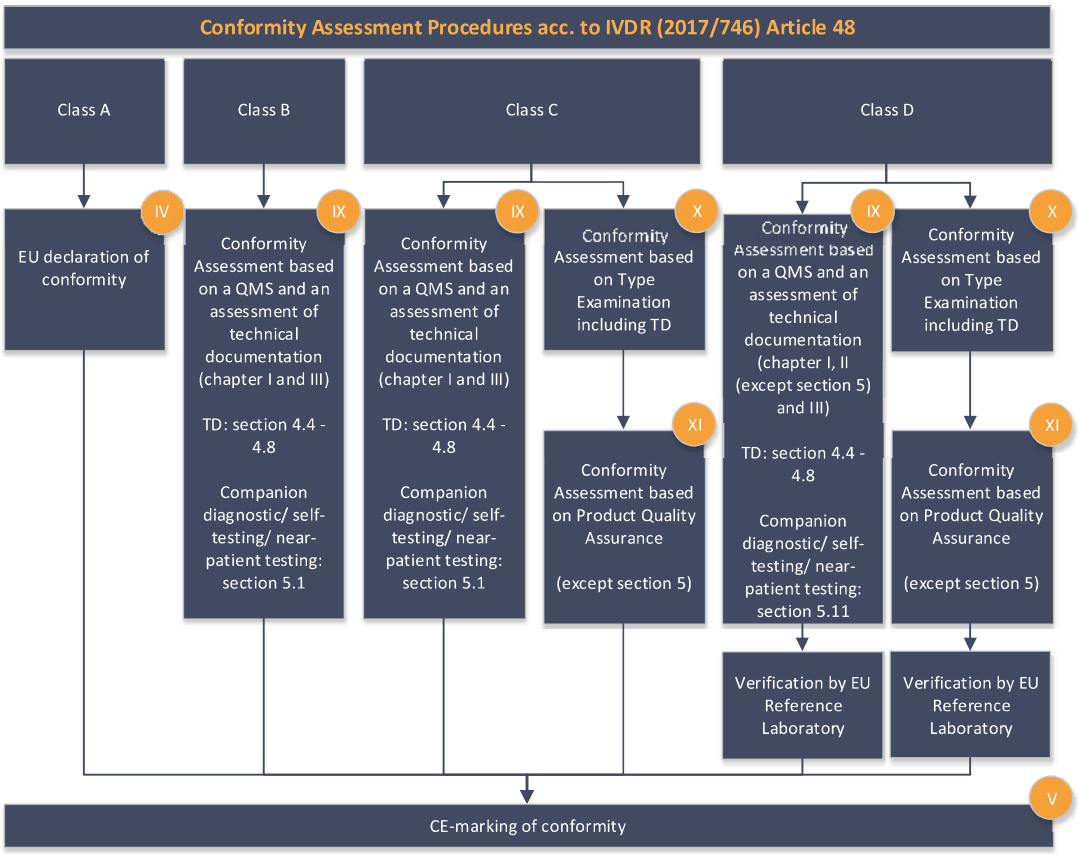

Figure 4: Conformity assessment procedures IVDR

6.1.5.1 Manufacturer Conformity Assessment

According to the IVDD, manufacturers of General IVDs must provide the EC declaration of conformity according to Annex III, what is applicable for the products produced by EXIAS Medical.

If the product is classified as a class A device, according to the rules of the IVDR, the manufacturer also must provide the EC declaration of conformity according to Annex IV after drawing up the technical documentation set out in Annexes II and III. This will be applicable for capillary tubes.

6.1.5.2 NB Conformity Assessment

A Notified Body is involved in the conformity assessment according to the IVDR for class B and C devices.

EXIAS Medical chooses the conformity assessment based on a QMS and an assessment of the technical documentation, since this conformity assessment procedure is applicable for both class B and class C devices and EXIAS Medical has installed a certified QMS according to the ISO 13485:2016. A Notified Body will than examine the conformity assessment and confirm the fulfillment of the demands of the IVDR.

6.1.6 #1.6: TD ok? / Pass Conformity Assessment?

If a Notified Body is involved in the conformity assessment procedure, the NB will check the TD. This check will take approximately 5 weeks depending on the capacity of the orders at the NB. Generally, the TDs are rejected and must be corrected. The second run will take again a couple of weeks. Therefore, the TD shall be created very precisely. The structure demanded by the NB shall be adhered too, to save time and resources.

6.1.7 #1.7: CE- marking of product

After the conformity assessment procedure is completed, the manufacturer can affix the CE marking according to IVDD Annex X. If the product is certified according to the IVDR, Annex V is applicable.
The mark shall be affixed visibly, legibly and indelibly to the device. This CE marking shall also appear on the instruction for use and any sales packaging.
If a Notified Body was involved in the conformity assessment procedure, identification number of the NB shall follow the CE marking.
This CE marking must be done before the product is placed on the market.

6.2 #2: Identify national regulatory requirements

The identification of countries where the product shall be placed on the market, is done according to the SOP_026_Marketing and Sales (see [7]).
After the CE- marking of conformity, additional national regulatory requirements must be met depending on the corresponding legislation. These additional requirements must be filled in the Regulatory Clearance Plan (RCP). Also, information about the national regulatory authority, the classification and information about the duration of the registration shall be filled in. This information can be found by research. Reliable sources are the homepages of EMERGO, the WHO or the homepages of the national regulatory authorities. The WHO provides papers for the regulatory systems at country level (see https://www.who.int/medical_devices/countries/regulations/en/). Here the main information about the national regulatory authority, classification system, registration need, post-market and premarket activities etc. can be found including weblinks for further information.

6.3 #3: Enter distributor information to RCP

Since EXIAS distributes its products via a network of distributors all over the globe, the distributors are responsible for the national registration and the communication with national regulatory authority. The distributors are managed by the QSP_013_Distributors Management (see [5]).

After signing a contract with a distributor, a list of registration requirements must be created by the distributors. These requirements can be documents or activities, which must be entered to the RCP.

6.4 #4: Create required documents/ Plan necessary activities

After the requirements are entered to the RCP, additional documents must be created, or the necessary activities planned. In the RCP there shall be a link to the requested record.

A document that is often required by States outside of the European Union, is the Free Sales Certificate (FSC). This documents must be requested from the BASG ("Bundesamt für Sicherheit und Gesundheitswesen") after the product has received the CE-marking of conformity. The FSC approves that the corresponding product is placed on the Austrian market so the market of the European Union lawfully. The FSC can be requested for more than one country at a time, so a collected request is reasonable for the avoidance of further costs. Generally, the FSC is valid for two years, if no change to the product has been made.
The current request form can be found under the following link:
https://www.basg.gv.at/en/medical-devices/forms-for-medical-devices/free-sales-certificate/

Along with the FSC request form, an excel sheet must be handed in, where corresponding products must be listed including the product descriptions, reference numbers and software versions.
The completion of the documentation of the FSC must be done very thoroughly. Depending on the application number, the waiting period is again approximately 5 weeks. If the application documents are incorrect, the documents must be sent in again and an additional waiting period must be expected.

Therefore, the following aspects are very important:

- It is very important, that there is no difference between the terms used on the request form and the excel sheet.
- The declaration of the product and product parts must be precise, a general declaration is not permitted.
- The intended use must emphasize, that the named product is indeed a medical device according to the law of medical devices (Medizinproduktegesetz MPG § 2).

– The manufacturer must be marked as manufacturer on all necessary documents with the correct and complete term of the companies` register including the complete address.

The costs for a FSC lie in the range between 501€ (1-10 states) up to 816€ (51-250 states) dependent on the number of states the certificate shall be provided for.

The FSC must be requested again after product changes. Further information about the FSC can be found at the homepage of the BASG (see https://www.basg.gv.at/en/medical-devices/free-sales-certificate-fsc/).

6.5 #5: Complete notarization of documents

Many states require the notarization by either a notary, embassy, or an apostilled certification of documents. This information must be communicated by the distributor.

The notarization by a notary is to be organized by the top management, since the notary must come to the company. If an additional notarization by either the embassy, the consulate or an apostilled certification of document is necessary, the document must be sent to the district court for approval.

The next step of notarization is the certification by the BMEIA ("Bundesministerium Europa, Integration und Äußeres"). Therefore, an accompanying letter must be created (see https://www.bmeia.gv.at/reise-aufenthalt/urkunden-und-beglaubigung-apostille/beglaubigung-apostille/kontakt/) and relevant fees will be charged. This notarization is also called an Apostille.

If the notarization must be done by the embassy, the document notarized by the BMEIA must be sent to the address of the embassy or consulate. This is conducted by sending a registered letter (see {4}) Note: embassy sometimes require cash for the notarization, which shall be sent with the postage service. Contacting the embassy or consulate is advised to get information about the payment terms.

6.6 #6: Complete registration activities

Created documents and activities must be fully completed before sending them to the distributor. Therefore, all documents must be checked with the Sales Manager and the top management. Only approved documents shall be sent to the responsible distributor.
If the feedback of the distributor is, that there are incorrect or missing documents, these documents must be corrected or generated and passed on to the distributor as fast as possible. The process owner is responsible to communicate the requests internally as well as to keep track of activities to fulfill those requests as soon as possible. If necessary the process owner has to inform top management to allocate enough internal resources. As soon as correct documents are sent, the distributor is responsible for the registration.

6.7 #7: Update RCP Status "registration completed"

After the distributors send the registration certificate or any similar confirmation of the national regulatory authority, that the product is placed on that market, the RCP Status is updated to "registration completed".

6.8 Reregistration

The distributor must name relevant reregistration activities if necessary. These activities must be planned and entered to the RCP. For the initiation of these activities, the process owner is in charge.

7 Training

- Responsible for the training of this Procedure: Process Owner
- Roles that must be trained within the company: Sales Manager, Top Management, Regulatory Compliance Manager, Quality Manager,
- Training material: the present SOP
- Frequency of training: once or after changes regarding the content of the SOP (editorial changes do require training)

8 Further applicable Documents

Nr.	Document / Title	Description
[1]	EM00_QSP_004_Regulatory Affairs	Procedure of screening and analyzing of regulatory requirements for products produced by EXIAS Medical
[2]	EM00_RCD_Essential Requirements Checklist	Checklist for fulfilling the Essential Requirements described in Annex I of the IVDD
[3]	EM00_RCD_Technical Documentation Checklist	Checklist for the creation of the Technical Documentation of EXIAS Medical products.
[4]	EM00_RCD_Regulatory Clearance Plan	Document for the tracing of the different regulatory requirements worldwide. This also includes general language requirements.
[5]	EM00_QSP_013_Distributors Management	Procedure for the management of distributors
[6]	SOP_034_Preparation of Project/Product documents	Guideline for preparing documents needed for regulatory compliance and project records
[7]	SOP_026_Marketing & Sales	Standard Procedure for Marketing and Sales activities

9 Appendix

Nr.	Appendix	Description
{1}	EU-Directive_98-79-EG	Directive on in vitro diagnostic medical devices
{2}	2017-746_IVDR_europe-in-vitro-diagnostic-regulation	Regulation on in vitro diagnostic medical devices
{3}	EM01_RCD_Product-Classification+Conformity-Assessment.docx	Documentation of the classification result of the product
{4}	EM00_Begleitschreiben_Embassy_certification	Document that accompanies the to be legalized documents for embassy certification

Doc Type	Annex II Regulatory Compliance Document
Title	EM00_RCD_Regulatory Clearance Plan
Project	EM00, EM01
Keywords	Regulatory Clearence, Product Registration, c|1 Analyzer
Description	This document describes the regulatory clearence plan for the product registration of products placed on the market by EXIAS Medical
	DRAFT
	Name Date Signature
Author	Magdalena Kodwani
Review	Gerald Nauschnegg
Approval	Udo Klinger

Change History

Rev. Nr.	Doc Vers.	Date	Editor	Concerning	Change Description
01	01	DRAFT	Magdalena Kedwani	All	Initial content

			# of Countries	11	62	64	1	60	28	61	50	71	55	19	59
					6-LATAM	6-LATAM	1-EUR	5-INCH	2-ME	5-INCH	4-APAC	6-LATAM	4-APAC	1-EUR	4-APAC
#		Regulatory Requirements	Detailed Requirements	# of States	Argentina	Brazil	Austria	China	Egypt	India	Indonesia	Mexico	Philippines	Romania	Vietnam
				Doc	x	x	x	x	x	x	x	x	x	x	x
1	General Requirements	Contact information manufacturer		3			1					A2		1	
		Letter of Authorization (LoA)		4	6						1	A1			3
		Distributor Contract		3					3		2		1		
		Free Sale Certificate (FSC)		7	6			1d)	2	4,1	4	B1			1
		Power of Attorney (PoA)		2				1e)		2					
		Self Declaration to Garantee Truthfulness of Documents Submitted by the manufacturer		1				13							
		Product Brochure		3								C	3		6
		contact information of responsible for placing the product on the market (EU)		2			3							3	
2	Conformity Assessment	CE	Certificate	6			2	1b)	1	5,2				2	7
		Declaration of conformity (DOC)	Statement that device complies with Essential Principles of Safety and Performance	2				1c)		5,4					
			A Statement that Conform to Medical Device management and related Law Regulation	1				12a)							
			A Statement that Conform to Medical Device Classification Regulation	1				12b)							
			A Statement that Conform to National Standard and Industry Standards	1				12c)							
3	QMS	ISO 13485	Certificate	6				1a)		5,1	3	C1	2		2
		Audit Report		1						4,3					
		PMS	Adverse Report Handling, FSCA, Complaint Management, Vigilance	1						7,21, 7,22, 7,23, 7,24					
		Risk Management	Produkt Risk Analysis	2				7			9				
			Risk Analysis Report	1						7,1					
		Test reports	EMC	1								J			
			IEEEC Certificate	1	5										
			Stability Test Data	3	3					7,17	6				
		Applied Standard List		1				12d)							

			# of Countries	11	62	64	1	60	28	61	50	71	55	19	59
					6-LATAM	6-LATAM	1-EUR	5-INCH	2-ME	5-INCH	4-APAC	6-LATAM	4-APAC	1-EUR	4-APAC
#		Regulatory Requirements	Detailed Requirements	# of States	Argentina	Brazil	Austria	China	Egypt	India	Indonesia	Mexico	Philippines	Romania	Vietnam
				Doc	x	x	x	x	x	x	x	x	x	x	x
4	Product Details	Device Masterfile	Device Masterfile	1						7					
			Brand name of device	2						7,1		A2			
			Executive summary	2				2a)		7,2					
			Substential Equivalance data with predicate device in india	1						7,3					
			Design Verification Report	1						7,7					
			Essential Requirements Checklist	2				2		7,9					
			Product Technical Requirements	1				8							
			Technical specifications	2				2c)				A2			
			Device Description	2				2b)				A2			
			Indications for use	1								A2			
			Analysis Description	1								A2			
			Qualitative and quantitative Composition of product	1	3										
			Diagrams, drawings,photographs, List of System Components	1								E			
			Scope of application and contraindications	1				2e)							
			Quality Control of finished product	1								I			
			List of Accessories and spareparts	1							15				
			Software verification and validation	1						7,16					
			Software Research	1				4g)							
		Certificate of Analysis (CoA)	Instrument	3						7,2	5	J			
			Reagents	1								J			
8	Performance Evaluation	Method comparisons		1								K			
		Product Performanc Study		1				4a)							
		Precision		1								K			
		Accuracy		1								K			
		Specificy		2							7	K			
		Sensitivity		2							7	K			
		Interference		1								K			
		Linearity Studies		1								K			
		Analytic Sensitiveness		1								K			
		Specimen correlation		1								K			
		Reference Material		1								M			
		Results/ Report		4	4			6		7,19		K			
5	Manufacturing procedure	Manufacturing flow chart		3				5		7,8		F			
		Plant Masterfile		1						6					
6	Product Information	Labeling and Packaging Details		4	2			11		7,4, 7,6		G,H			
		Packet of reagent Photo	include part of the pack, 6 sides	1							11				
		IFU		6	1			9, 10		7,5	10	D	4		
		Storage Conditions		1								A2			
		Safety information/ short guidance in designated languages		1				4e)							
7	Bio compatibility	Biocompatibility Protocol and Report		1						7,11					
		Biological Compativility Evaluation Research		1				4b)							
		Biological Safety Study		2				4c)		7,13					

			Registration time line				Product Information					
#	Region	Country	Start Activities	duration of registration (months)	Regsitration completet (calculated)	FCM	national regulatory authority	Classification	Registration Status	FSC	# Notarial certification	
											Doc	Status
62	6-LATAM	Argentina	Jun.19	6	Dez.19	N	- Direccion de Tecnologia Medica, Administracion National de Medicos, Alimentos y Tecnologia Médico (ANMAT)	open	investigation in progress	x	LoA	open
											FSC	open
											Distibutor contract	completed
1	1-EUR	Austria	Mai.19	2	Jul.19	J	- MPG / IVDD - Bundesamt für Sicherheit und Gesundheitswesen (BASG)	IVDD: General IVD	investigation completet	n.a.	n.a.	n.a.
64	6-LATAM	Brazil	Mai.19	12	Mai.20	N	- brasilianisches Gesetz No. 6360/1976 und Decree 74.094/77 - Agencia National de Vigilancia Santaria (ANVISA)	Class II - Cadastro Route	investigation in progress	open	open	open
60	5-INCH	China	Mai.19	18	Nov.20	N	NMPA (National Medical Product Administation) formerly known as SDA, SFDA und CFDA	open	investigation in progress	x	Distributor contract	completed
											ISO	open
											CE	open
											DoC	open
											FSC	open
											PoA	open
											2	open
											3	open
											4	open
											5	open
											Clinical Eval	open
											Produkt Risk Analysis	open
											Technical Requ	open
											english IFU	open
											chinese IFU	open
											label	open
											12	open
											13	open

			Registration time line				Product Information					
#	Region	Country	Start Activities	duration of registration (months)	Regsitration completet (calculated)	FCM	national regulatory authority	Classification	Registration Status	FSC	# Notarial certification	
											Doc	Status
28	2-ME	Egypt	Jul.19	2	Sep.19	N	CAPA (Central Administration of Pharmaceutical Affairs.	n.a. (no registration necessary)	investigation completet	x	Distributor contract	open
61	5-INCH	India	Apr.19	12	Apr.20	N	- Central Drugs Standard Control Organisation (CDSCO)	Class B	investigation completed	x	PoA	open
											FSC	open
											ISO	open
											CE	open
											DOC	open
50	4-APAC	Indonesia	Feb.19	6	Aug.19	N	- Directorate General of Pharmaceutical and Medical Devices, The Ministry of Health of the Republic of Indonesia - ASEAN	IVD Class B	investigation completed	x	Distributor contract	completed
											LoA	open
71	6-LATAM	Mexico	Jul.19	16	Nov.20	N	- Comision Federal para la Protection contra Riegos Sanitarios (COFEPRIS)	Agentes de diagnóstico de uso in vitro - Clase II	investigation completet	x	LoA	open
											FSC	open
											ISO	open
55	4-APAC	Philippines	Mai.19	6	Nov.19	J	- FDA of Philippines - ASEAN	IVD Class B	investigation completet	n.a.	Distributor contract	completed
19	1-EUR	Romania	Apr.19	2	Jun.19	J	- IVDD - law on medical devices (L176/2000) - NAMMD (National Agency for Medicines and Medical Devices)	IVDD: General IVD	investigation completet	n.a.	n.a.	n.a.
59	4-APAC	Vietnam	Jul.19	2	Sep.19	N	- Department of Medical Equipment and Health Works - ASEAN	Class B	investigation completet	x	open	open

									Registration	
#	Region	Country	# Apostilles		# Embassy certification		Status of notarization	Specific requirements	Registration date	Re- registration
			Doc	Status	Doc	Status				
62	6-LATAM	Argentina	LoA	open	0	n.a.	open	- label and instructions must be presented in spanish		5 years
			FSC	open	0	n.a.				
			0	n.a.	0	n.a.				
1	1-EUR	Austria	n.a.	n.a.	n.a.	n.a.	n.a.	- Country on origin of manufacturer - Acc. IVDD - Declaration of conformity by manufacturer - Medizinprodukteregistereintrag		IVDD will expire on the 26th of May 2022. Until then an adaption to the IVDR must be completet.
64	6-LATAM	Brazil	open	open	open	open	open	- payment proof to TFVS through GRU - compliance with BGMP - product labeling shall be in (brazilian) portuguese or use appropriate symbols - IFU shall be in (brazilian) portuguese - technical description may be exempt from translation		5 years
60	5-INCH	China	0	n.a.	0	n.a.	in progress	- (see Appendix) - the letter of authorisation shall be written by the applicant to the legal agent in China, by applicant to representing agent and by applicant to PM Service Agent in China - Device must have been placed on the market in different country. - UM in Mandarin - Acc. Book Harer In China registraion takes more than 18 months. The NMPA is a big challange. Detailed examples of the device must be handed out as well as precise data.		5 years
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				

									Registration	
#	Region	Country	# Apostilles		# Embassy certification		Status of notarization	Specific requirements	Registration date	Re- registration
			Doc	Status	Doc	Status				
28	2-ME	Egypt	Distributor contract	open	Distributor contract	open	open	- very likely to EU registration. - IVDs are not subjected to registration - IVDs only require an import permit and a sample analysis for a number of kits - distributors handle this process in full		5 years
61	5-INCH	India	PoA	open	0	n.a.	open	- Form 20B and 21B/21C must be handed in by the distributor - latest audit report - since 2017 new regulatory system, classification A-D dependent on list.		does not expire
			FSC	open	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
			0	n.a.	0	n.a.				
50	4-APAC	Indonesia	Distributor contract	completed	Distributor contract	completed	in progress	- Introduction to IVD, Intended Use - Commercial marketing history - describtion of intended use and indication		open
			LoA	open	LoA	open				
71	6-LATAM	Mexico	LoA	open	0	n.a.	open	- technical information describing characterisitics of MD must be submitted in spanish -accepting USA FDA and Canada registration - Product Brochure and IFU in spanish		open
			FSC	open	0	n.a.				
			ISO	open	0	n.a.				
55	4-APAC	Philippines	Distributor contract	in progress	Distributor contract	open	in progress	- Application form from distributor (notarized) - production overview - Brand name (if branded products) - Evidence of registration fee		1 year (initial registration) 5 years (else)
19	1-EUR	Romania	n.a.	n.a.	n.a.	n.a.	n.a.	- no further registration with CE (only registration of Manufacturer or representive) - check if language requirements are met		IVDD will expire on the 26th of May 2022. Until then an adaption to the IVDR must be completet.
59	4-APAC	Vietnam	open	open	open	open	open	open		open

Language Requirement

#	Zone	Country	Official Language	IFU	GUI texts	Packaging label
62	6-LATAM	Argentina	Spanish	Spanish	Spanish	Spanish
1	1-EUR	Austria	German	German	German	German
64	6-LATAM	Brazil	Portuguese (bra)	Portuguese (bra)	Portuguese (bra)	Portuguese (bra)
60	5-INCH	China	Chinese	Chinese and English	Chinese	Chinese
28	2-ME	Egypt	Arabic	English	English	English
61	5-INCH	India	Hindi, English	English	English	English
50	4-APAC	Indonesia	Indonesian	English	English	English
71	6-LATAM	Mexico	Spanish	Spanish	Spanish	Spanish
55	4-APAC	Philippines	Filipino, English	English	English	English
19	1-EUR	Romania	Romanian	Romanian	English	English
59	4-APAC	Vietnam	Vietnamese	English	English	English