Regulations and Directives—Past, Present, Future

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Abstract Regulations are binding acts which are obligatory in the European Union. All members of the European Union must apply Regulations. On the other hand, there are Directives, legislative acts which represent the base setting the goal which has to be achieved by EU countries for a specific area. Each EU country has individual national laws in order to achieve that goal. Directives which regulate harmonized products in the EU are known as New Approach Directives. One of the Directives which belong to the group of the New Approach is Directive 93/42/EEC on medical devices. The integral part of a Directive is Harmonised Standard which serves Manufacturers, other economic operators, or conformity assessment bodies to demonstrate that products, services, or processes comply with relevant EU legislation. Conformity assessment is a process that is performed by the manufacturer in order to demonstrate if all specific requirements related to the product have been met. Conformity assessment is provided by a competent body (notified bodies) and differs for different classification of medical devices. There are different approaches in conformity assessment of medical devices in the EU and USA which are described in this chapter. Many European countries have recognised the importance of metrology and its influence in providing services which will ensure accurate and precise measurements of medical devices that have a measurement function.

1 Introduction

EU legislation is divided into two levels with primary legislation embodied by the treaties, and secondary legislation given in the form of regulations, directives and decisions which are used to implement the policies set out within the treaties [1].

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Secondary legislation is made by the EU institutions. It is the third major source of Community law after the treaties (primary legislation) and international agreements. It comprises:

- binding legal instruments (regulations, directives and decisions)
- non-binding instruments (resolutions, opinions).

EUR-Lex provides free access to EU law and other documents considered to be public. The content on the official website is available in 24 official languages of the European Union.

This chapter has the purpose to describe the legislation used in EU in the field of medical devices, and the approaches to be followed by producers (manufacturer) of medical devices in order to be approved and placed in the EU market.

In order to increase safety in the production of medical devices, manufacturers have to follow the relevant legislation. This legislation in the EU is given through the directives and regulations followed by appropriate harmonized standards set out in the directives. In addition to the stated documentation, there are also other acts of European Union Law.

The description and meaning of legal acts in accordance with EU law is given bellow [2]:

A "**regulation**" is a binding legislative act. It must be applied in its entirety across the EU.
A "**directive**" is a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals.
A "**decision**" is binding on those to whom it is addressed (e.g. an EU country or an individual company) and is directly applicable.
A "**recommendation**" is not binding. When the Commission issued a recommendation that EU countries' law authorities improve their use of videoconferencing to help judicial services work better across borders, this did not have any legal consequences. A recommendation allows the institutions to make their views known and to suggest a line of action without imposing any legal obligation on those to whom it is addressed.
An "**opinion**" is an instrument that allows the institutions to make a statement in a non-binding fashion, in other words without imposing any legal obligation on those to whom it is addressed. An opinion is not binding. It can be issued by the main EU institutions (Commission, Council, Parliament), the Committee of the Regions and the European Economic and Social Committee. While laws are being made, the committees give opinions from their specific regional or economic and social viewpoint.

Review of EU legislation [3] can be made via the official website of EU which is especially dedicated to this issue, http://eur-lex.europa.eu.

An integral part of the directives are harmonised standards.

A **harmonised standard** [4] is a European standard developed by one of the recognised European Standards Organisation: CEN [5], CENELEC [6], or ETSI [7]. It is created following a request from the European Commission to one of these organisations. Manufacturers, other economic operators, or conformity assessment bodies can use harmonised standards to demonstrate that products, services, or processes comply with relevant EU legislation.

The references of harmonised standards must be published in the Official Journal of the European Union. The purpose of this website is to provide access to the latest lists of references of harmonised standards and other European standards published in the Official Journal of the European Union (OJEU).

Medical devices

This chapter describes the approach of placing medical devices in the EU market, the process of approval in accordance with appropriate EU directive, the role of notified bodies, processes of conformity assessment, comparison with approach used in USA and the role of medical devices under the frame of Legal Metrology.

A "**medical device** [8]" is any instrument, apparatus, appliance, material or other item, whether used separately or combined with another device, including the software necessary for its proper application intended by the manufacturer intended for human use for the purpose of:

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

2 Placing of Medical Devices in the Market of EU in Accordance with EU Legislation

Before the placing of a medical device in the market, implying that it is ready for use, the device has to be approved by competed body providing conformity assessment of a tested subject with appropriate reference. There are different recognized approaches in the process of approval.

In most countries medical devices are categorized based on the risks associated with their use, and the approval process varies by category [9]. In some countries like the United Kingdom, manufacturers of low-risk devices may register with the government agency and simply declare that the devices meet the requirements to be approved, but devices classed as higher risk must undergo a more detailed review performed by a notified body. In most cases within the EU the approach of putting

the medical device in the market is similar, but it differs if compared with the approach used in the USA, which will be described later in this paper.

Medical Device Approval Process in EU

Medical devices must comply with the rules established by EU directives related to medical devices prior to being put in the market and/or put into service in the EU, the European Economic Area, or Switzerland. At EU level, there is no centralized approach similar to that in the United States.

The European Medicines Agency [10], unlike the Federal Drug Administration in the United States, is not involved in the approval process of medical devices. Manufacturers, prior to placing their devices in the market, are required to determine the classification of a device, based on the risk factors associated with each device, and then to apply the appropriate conformity route. Medical devices are assessed for efficiency and safety by notified bodies, generally private organizations, staffed by experts and certified by the EU Member States. In the final stage, medical devices, with some exceptions for such things as custom made devices and devices intended for clinical investigation, are given a CE marking, which ensures that medical devices are in conformity with EU rules and are ready to be marketed.

3 EU Legislation in the Field of Medical Devices

Legislation in the field of medicine in the European Union, i.e. legislation relating to medical devices, is based on Council Directive **93/42/EEC** of 14 June 1993. This directive further relies on the following directives [10]:

- Directive **93/68/EEC** (CE Marking);
- Directive **98/79/EC** of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices;
- Directive **2000/70/EC** of the European Parliament and of the Council of 16 November 2000 amending Council Directive 93/42/EEC as regards to medical devices incorporating stable derivates of human blood or human plasma;
- Directive **2001/104/EC** of the European Parliament and of the Council of 7 December 2001 amending Council Directive 93/42/EEC concerning medical devices;
- Directive **2007/47/EC** of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market.

In the past, one more directive was in force, but it has been repealed as of January 1, 1995. This was the Council Directive **76/764/EEC** on the approximation of the laws of the member states on clinical mercury-in-glass, maximum reading thermometers.

As mentioned in the introduction, beside directives, there are a great number of written standards used in manufacturing of medical devices.

In the field of medical devices, there are ca. 200 standards which have been issued under the European Committee for Standardization CEN (without revision), and close to 100 standards issued under the European Committee for Electrotechnical Standardization CENELEC (without revision) [11]. Taking into account such a large number of standards regulating the requirements for a particular product group, it is easy to conclude that this area of manufacturing presents an area where most attention is paid in relation to the safety of the product itself and its users.

EU Directive 93/42/EEC

The most comprehensive application in the field of medical devices of all directives mentioned in the text above has been the Directive 93/42/EEC which is the basis for the production of medical devices, and other directives complementing this field. This Directive was first published in the year 1993 and till 2007 it has been reviewed several times. Revisions of Directive 93/42/EEC were published in the following years:

- 12/07/1993
- 07/12/1998
- 13/12/2000
- 10/01/2002
- 20/11/2003
- 11/10/2007.

Directive 93/42/EEC belongs to the group of the New Approach directives, meaning that the products regulated by this Directive fall within the group of harmonized products in the EU. The application of the directive is a legal requirement for all manufacturers of medical devices in EU.

New Approach is a regulatory technique used for removing technical barriers to trade in Europe. For this purpose a common set of harmonised technical regulations were implemented in the member countries of the EU and in some non-member countries as well. The number of directives based fully or partially on the principles of New Approach is 30 [12].

Each New Approach directive stipulates the essential requirements, such as product safety or reliability which are to be satisfied by the product. Products, which satisfy these conditions, may be sold freely inside and among the European countries. New Approach directives have a binding effect as to the goals set up in them, but the member states can choose the methods to reach these goals in their national legislation.

In accordance with the directives of the New Approach, the manufacturer represents a natural or legal person responsible for the design or manufacture and release of the product in the EU market under his/her name or his/her trade name.

The New Approach directives apply to products which are intended to be released on the EU market. In order to put the product on the market, it has to be

assessed for conformity with the requirements defined by the specific directive. If the product, which is a subject of the conformity assessment, must satisfy the requirements of other directives, then the conformity assessment has to also be performed in accordance with those other directives.

In relation to the conformity assessment the manufacturer has certain responsibilities, reflected depending on the applied procedures. The manufacturer must take all necessary measures to ensure that the production process satisfy conformity of the product in order to set the CE mark on the product, which includes drawing technical documentation and creating EC[1] declaration of conformity. Depending on the directive, it is possible to claim from the manufacturer to submit products for testing and certification by a third party (usually a notified body) or to certify quality system by a notified body.

4 Notified Bodies for Conformity Assessment According to Directive 93/42/EEC

In the phase of the production, Medical devices are subject of compliance with certain directives and standards. Currently, in Europe, the most applied EU Directives for the production of measuring devices are 90/385/EEC, 93/42/EEC and 98/79/EEC (including the revision of 2007/47/EEC). The greatest responsibility in the production of medical devices holds the manufacturer himself, who has to ensure that the product meets the applicable legal requirements and, on the other hand, there is a notified body for conducting conformity assessment appointed by EU governments and with the obligation to validate and ensure that the product fulfil all the relevant requirements prescribed by the relevant directives.

At the moment, NANDO [13] database comprises 58 registered bodies competent to perform conformity assessment of medical devices in accordance with Directive 93/42/EEC. The highest number of notified bodies comes from Germany, 11 of them to be exact. Notified bodies perform tasks related to conformity assessment procedures, according to the applicable harmonized technical legislation when it requires the participation of a third party. Notified bodies may offer their services in the EU, but also to the third countries.

[1] As part of conformity assessment, the manufacturer or the authorised representative must draw up a Declaration of conformity (DoC). The declaration should contain all information to identify:

- the product
- the legislation according to which it is issued
- the manufacturer or the authorised representative
- the notified body if applicable
- a reference to harmonised standards or other normative documents, where appropriate.

5 Conformity Assessment of Medical Devices

Conformity assessment is a process that is performed by the manufacturer in order to demonstrate if all specific requirements related to the product have been met. The product itself is subject to conformity assessment in the stages of design and production. EU directives require the conduction of the process composed of one or two modules of conformity assessment. Conformity assessment of medical devices in accordance with Directive 93/42/EEC shall be carried out in accordance with the classification of the device itself.

In accordance with the directive 93/42/EEC, all medical devices are divided into four accuracy classes of increased risk. Accuracy classes of medical devices and related conformity assessment procedure in accordance with directive 93/42/EEC are given in Table 1 [14].

Products must be designed and manufactured in such a way that when used under proscribed conditions and for the intended purpose, they do not compromise neither patient safety, nor security and health of other users.

Medicinal products for the purpose of conformity assessment procedures, and for the given level of risk for the user, are divided into:

- Class I—medical devices with a low level of risk for the user,
- Class IIa—medical devices with a higher degree of risk for the user,
- Class IIb—medical devices with a high degree of risk for the user,
- Class III—medical devices with the highest degree of risk for the user.

This classification is done in accordance with the Annex IX of Directive 93/42/EEC. Classification rules are based on the sensitivity of the human body, taking into account the possible risks associated with the technical production and manufacture of medical devices.

Products must be in compliance with the essential requirements set out in Annex I of Directive 93/42/EEC which applies to them, taking into account the purpose of use of these products.

Table 1 Accuracy classes of medical devices and related conformity assessment procedure

Conformity assessment procedures	Classes					
Annexes	I	I sterile	I measure	IIa	IIb	III
II (+ section 4)						√
II (− section 4)		√	√	√	√	
III					√	√
IV		√	√	√	√	√
V		√	√	√	√	√
VI		√	√	√	√	
VII	√	√	√	√		

Table 2 Annexes to be applied depending on the class of medical device

Annex II	EC declaration of conformity (full quality assurance system) with or without examination of the design of the product
Annex III	EC type examination
Annex IV	EC verification
Annex V	EC declaration of conformity (production quality assurance)
Annex VI	EC declaration of conformity (product quality assurance)
Annex VII	EC declaration of conformity

Depending on the accuracy class of increased risks of medical devices, different procedures of conformity assessment in accordance with the Annexes of Directive can be applied. Annexes to be applied depending on the class are given in Table 2.

Technical documentation relating to the products of class IIa and IIb shall be examined by the notified body based on the program of a representative sample in the context of Annex II, V and VI of Directive 93/42/EEC.

As found in NANDO database, under Directive 93/42/EEC conformity assessment can be performed on the following products:

- General non-active, non-implantable medical devices
- Non-active devices for anaesthesia, emergency and intensive care
- Non-active devices for injection, infusion, transfusion and dialysis
- Non-active orthopaedic and rehabilitation devices
- Non-active medical devices with measuring function
- Non-active ophthalmologic devices
- Non-active instruments
- Contraceptive medical devices
- Non-active medical devices for disinfecting, cleaning, rinsing
- Non-active devices for in vitro fertilisation (IVF) and assisted reproductive technologies (ART)
- Non-active medical devices for ingestion
- Non-active implants
- Non-active cardiovascular implants
- Non-active orthopaedic implants
- Non-active functional implants
- Non-active soft tissue implants
- Devices for wound care
- Bandages and wound dressings
- Suture material clamps
- Other medical devices for wound care
- Non-active dental devices and accessories
- Non-active dental equipment and instruments
- Dental materials
- Dental implants
- General active medical devices

- Devices for extra-corporal circulation, infusion and haemopheresis
- Respiratory devices, devices including hyperbaric chambers for oxygen therapy, inhalation anaesthesia
- Devices for stimulation or inhibition
- Active surgical devices
- Active ophthalmologic devices
- Active dental devices
- Active devices for disinfection and sterilisation
- Active rehabilitation devices and active prostheses
- Active devices for patient positioning and transport
- Active devices for in vitro fertilisation (IVF) and assisted reproductive therapy (ART)
- Software
- Medical gas supply system and parts thereof
- Devices for imaging
- Imaging devices utilising ionizing radiation
- Imaging devices utilising non-ionizing radiation
- Monitoring devices
- Monitoring devices of non-vital physiological parameters
- Monitoring devices of vital physiological parameters
- Devices for radiation therapy and thermo therapy
- Devices utilising ionizing radiation
- Devices utilising non-ionizing radiation
- Devices for hyperthermia/ hypothermia
- Devices for (extracorporeal) shock-wave therapy (lithotripsy).

Horizontal Technical Competences

- Medical devices incorporating medicinal substances according to Directive 2001/83/EC
- Medical devices utilising tissues of animal origin, including Regulation 722/212 (Directive 2003/32/EC up to 28.08.2013)
- Medical devices incorporating derivates of human blood, according to Directive 2000/70/EC, amended by Directive 2001/104/EC
- Medical devices referencing the Directive 2006/42/EC on machinery
- Medical devices in sterile condition
- Medical devices utilising micromechanics
- Medical devices utilising nanomaterials
- Medical devices utilising biological active coatings and/or materials or being wholly or mainly absorbed
- Medical devices incorporating software/utilising software/controlled by software.

In the "Blue Guide" [15] on the implementation of EU rules on the products, the modules that are used to carry out conformity assessment are listed. In total, there are eight modules labelled with letters A through H. Modules specify responsibilities of the manufacturer and level of participation of in-house accredited bodies or notified bodies for conformity assessment. It is important to notice that an in-house body cannot act as a notified body, but they must demonstrate the same technical competence and impartiality to external bodies through accreditation as notify bodies. Conformity assessment bodies which carry out the assessment in accordance with modules that are shown in flow-chart (below) for the medical devices must meet the implementation of certain international standards (EU standards), or a combination of them.

The respective standards are: EN ISO/IEC 17020 (Requirements for the operation of various types of bodies performing inspection), EN ISO/IEC 17021 (Requirements for bodies providing audit and certification of management systems) and EN ISO/IEC 17065 (Requirements for bodies certifying products, processes and services) which are focused on criteria of conformity assessment, while standard EN ISO/IEC 17025 (General requirements for the competence of testing and calibration laboratories) deals with aspects of testing and calibration.

Bodies performing conformity assessment shall be accredited by the national accreditation body for specified standards. Accreditation implies confirmation of competences of the third party to an authority that may perform conformity assessment, respectively conformity with the requirements of applicable standards and additional requirements for the subject matter. Not all conformity assessment notified bodies from the NANDO base for the Directive 93/42/EEC have accredited their services. Some of them have confirmed their competences (they have been assessed) in accordance with Commission Implementing Regulation (EU) No 920/2013 [16]. In this case, assessment is performed by designating authorities [16] and joint assessment teams, which is built from the pool of national expert assessors made available from all of the designating authorities.

Setting out the requirements for accreditation and market surveillance relating to the marketing of products is done by Regulation 765/2008/EC [17], which should be seen as a complementary to Decision 768/2008/EC (on a common framework for the marketing of products). Accreditation provides authoritative statement about technical competence of bodies whose task is to ensure conformity with the applicable requirements.

The following Table 3 show modules in accordance with the "Blue guide", their description and related standards which have to be applied (or combination) in order to fulfil requirements of conformity assessment (Fig. 1).

Table 3 Overview of modules

Module	Description of the module	Applicable standards
A Internal production control	Covers both design and production The manufacturer himself ensures the conformity of the products to the legislative requirements (no EU-type examination)	EN ISO/IEC 17025 (+ ability to decide on conformity), or EN ISO/IEC 17020, EN ISO/IEC 17025 to be taken into account for testing required, or EN ISO/IEC 17065, EN ISO/IEC 17025 to be taken into account for testing required
A1 Internal production control plus supervised product testing	Covers both design and production. A + tests on specific aspects of the product carried out by an in-house accredited body or under the responsibility of a notified body chosen by the manufacturer	
A2 Internal production control plus supervised product checks at random intervals	Covers both design and production. A + product checks at random intervals carried out by a notified body or an in-house accredited body	
B EU-type examination	Covers design. It is always followed by other modules by which the conformity of the products to the approved EU-type is demonstrated. A notified body examines the technical design and/or the specimen of a type and verifies and attests that it meets the requirements of the legislative instrument that apply to it by issuing an EU-type examination certificate. There are 3 ways to carry out an EU-type examination: (1) production type, (2) combination of production type and design type and (3) design type	EN ISO/IEC 17020, EN ISO/IEC 17025 to be taken into account for testing required, or EN ISO/IEC 17065, EN 17025 to be taken into account for testing required
C Conformity to EU-type based on internal production control	Covers production and follows module B Manufacturer must internally control its production in order to ensure product conformity against the EU-type approved under module B	EN ISO/IEC 17025 (+ ability to decide on conformity), or EN ISO/IEC 17020, EN ISO/IEC 17025 to be taken into account for testing required, or

(continued)

Table 3 (continued)

Module	Description of the module	Applicable standards
C1 Conformity to EU-type based on internal production control plus supervised product testing	Covers production and follows module B. Manufacturer must internally control its production in order to ensure product conformity against the EU-type approved under module B. C + tests on specific aspects of the product carried out by in-house accredited body or under the responsibility of a notified body chosen by the manufacturer (*)	EN ISO/IEC 17065, EN ISO/IEC 17025 to be taken into account for testing required
C2 Conformity to EU-type based on internal production control plus supervised product checks at random intervals	Covers production and follows module B. Manufacturer must internally control its production in order to ensure product conformity against the EU-type approved under module B. C + product checks at random intervals tests on specific aspects of the product carried out by a notified body or in-house accredited body	
D Conformity to EU-type based on quality assurance of the production process	Covers production and follows module B. The manufacturer operates a production (manufacturing part and inspection of final product) quality assurance system in order to ensure conformity to EU type. The notified body assesses the quality system	EN ISO/IEC 17021 (+ product related knowledge) or EN ISO/IEC 17065
D1 Quality assurance of the production process	Covers both design and production. The manufacturer operates a production (manufacturing part and inspection of final product) quality assurance system in order to ensure conformity to legislative requirements (no EU-type, used as in module D without module B). The notified body assesses the production (manufacturing	

(continued)

Table 3 (continued)

Module	Description of the module	Applicable standards
	part and inspection of final product) quality system	
E Conformity to EU-type based on product quality assurance	Covers production and follows module B. The manufacturer operates a product quality (= production quality without the manufacturing part) assurance system for final product inspection and testing in order to ensure conformity to EU-type. A notified body assesses the quality system. The idea behind module E is similar to the one under module D: both are based on a quality system and follow module B. Their difference is that the quality system under module E aims to ensure the quality of the final product, while the quality system under module D (and D1 too) aims to ensure the quality of the whole production process (that includes the manufacturing part and the test of final product). E is thus similar to module D without the provisions relating to the manufacturing process	EN ISO/IEC 17021(+ product related knowledge) or EN ISO/IEC 17065
E1 Quality assurance of final product inspection and testing	Covers both design and production. The manufacturer operates a product quality (= production quality without the manufacturing part) assurance system for final product inspection and testing in order to ensure conformity to the legislative requirements (no module B (EU-type), used like E without module B). The notified body assesses the quality system. The idea behind module E1 is similar to the one under module D1: both are based on a quality system. Their difference is that the quality system under	

(continued)

Table 3 (continued)

Module	Description of the module	Applicable standards
	module E1 aims to ensure the quality of the final product, while the quality system under module D1 aims to ensure the quality of the whole production process (that includes the manufacturing part and the test of final product). E1 is thus similar to module D1 without the provisions relating to the manufacturing process	
F Conformity to EU-type based on product verification	Covers production and follows module B. The manufacturer ensures compliance of the manufactured products to approved EU-type. The notified body carries out product examinations (testing of every product or statistical checks) in order to control product conformity to EU-type. Module F is like C2 but the notified body carries out more systematic product checks	EN ISO/IEC 17025 (+ ability to decide on conformity), or EN ISO/IEC 17020, EN 17025 to be taken into account for testing required, or EN ISO/IEC 17065, EN 17025 to be taken into account for testing required
F1 Conformity based on product verification	Covers both design and production. The manufacturer ensures compliance of the manufactured products to the legislative requirements. The notified body carries out product examinations (testing of every product or statistical checks) in order to control product conformity to the legislative requirements (no EU-type, used like F without module B) Module F1 is like A2 but the notified body carries out more detailed product checks	
G Conformity based on unit verification	Covers both design and production. The manufacturer ensures compliance of the manufactured products to the legislative requirements. The	EN ISO/IEC 17020, EN 17025 to be taken into account for testing required, or EN ISO/IEC 17065, EN

(continued)

Table 3 (continued)

Module	Description of the module	Applicable standards
	notified body verifies every individual product in order to ensure conformity to legislative requirements (no EU-type)	17025 to be taken into account for testing required
H Conformity based on full quality assurance	Covers both design and production. The manufacturer operates a full quality assurance system in order to ensure conformity to legislative requirements (no EU-type). The notified body assesses the quality system	EN ISO/IEC 17021 (+ product related knowledge)
H1 Conformity based on full quality assurance plus design examination	Covers both design and production. The manufacturer operates a full quality assurance system in order to ensure conformity to legislative requirements (no EU-type). The notified body assesses the quality system and the product design and issues an EU design examination certificate. Module H1 in comparison to module H provides in addition that the notified body carries out a more detailed examination of the product design. The EU-design examination certificate must not be confused with the EU-type examination certificate of module B that attests the conformity of a specimen 'representative of the production envisaged', so that the conformity of the products may be checked against this specimen. Under EU design examination certificate of module H1, there is no such specimen. EU design examination certificate attests that the conformity of the design of the product has been checked and certified by a notified body	EN ISO/IEC 17021 (+ product related knowledge) or EN ISO/IEC 17065 or EN ISO/IEC 17020, EN 17025 to be taken into account for testing required

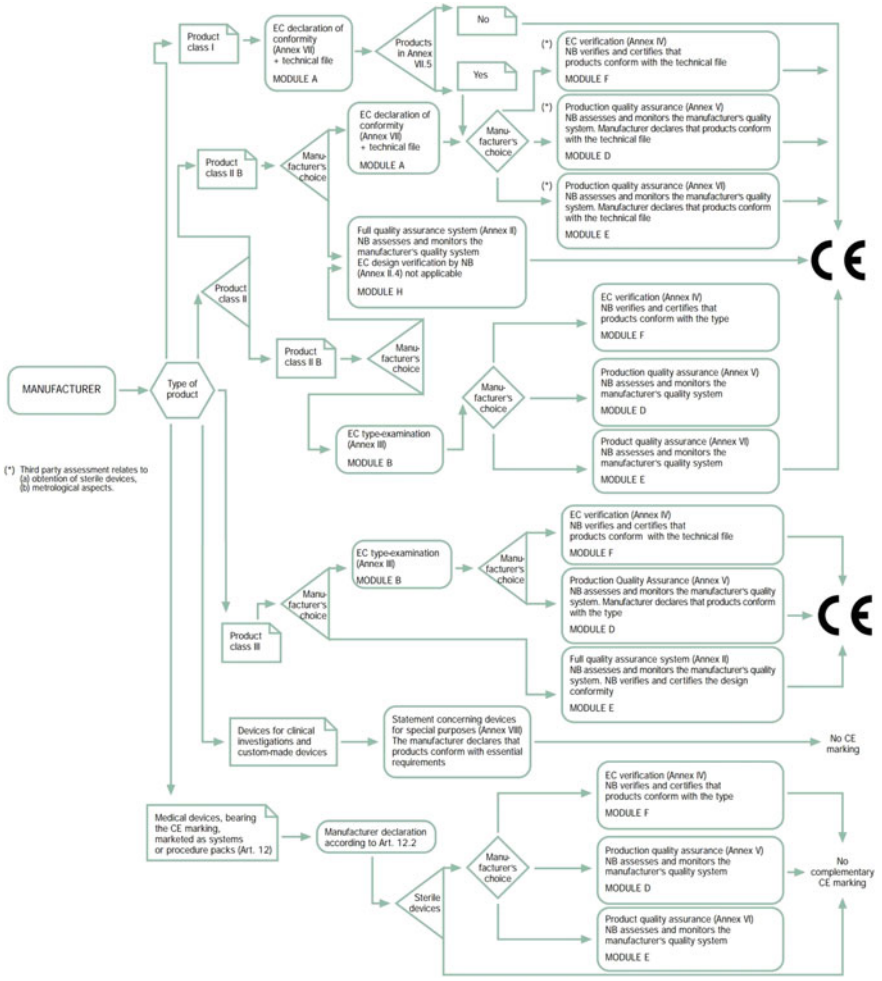

Fig. 1 Flow chart for the conformity assessment procedures provided for Directive 93/42/EEC on medical devices [18]

6 Standards Used in Manufacturing Process of Medical Devices

New Approach regulations are accompanied by a wide range of harmonised European standards. The New Approach regulatory technique is distinguished from other regulatory techniques by the relationship between regulations and standards: while the compliance with regulations is mandatory, the application of harmonised standards is in case of most New Approach directives voluntary [19].

Harmonized standards are European Norms (EN) elaborated by the European standardization bodies (CEN, CENELEC, ETSI) under a mandate from the European Commission. The Commission specifies certain essential requirements within a given directive that have to be set out in greater detail. It subsequently mandates and partially finances the development of standards that specify these details [20].

One of the most widely used standards in the area of manufacturing of the medical devices is the standard IEC 60601-1 Medical electrical equipment—Part 1: General requirements for basic safety and essential performance.

Standard IEC 60601-1 is a basic document comprised of two parts that relate to the safety of medical devices (collateral standards) and to various types of medical equipment (particular standards). The basic version of the standard was published for the first time in 1977 and was related to the issues of electrical and mechanical safety.

Standards marked with IEC 60601-1-X are collateral standards (where X represents sub-standards, altogether 11).

Standards marked with IEC 60601-2-X are specific standards (where X represents sub-standards, altogether 58).

The basic standard IEC 60601-1 is applied for the purpose of basic safety and essential performance of Medical Electronical Equipment and Medical Electrical Systems. The content of the standard describes protection against electrical Hazards from Medical Electrical Equipment, protection against mechanical Hazards of Medical Electrical Equipment and Medical Electrical Systems, protection against unwanted and excessive radiation Hazards, and protection against excessive temperatures and other Hazards.

In this part of the chapter the main activities on protection against electrical Hazards from Medical Electrical Equipment will be described, since the patients and operators are exposed to this hazard the most when operating or using the equipment which did not fulfil the requirements stated in the corresponding standard. Requirements set in the standard IEC 60601-1 give the manufacturer a possibility to better understand how to reduce risks of harm or to bring them to the acceptable limits.

Protection against electrical Hazards from Medical Electrical Equipment in accordance with standard IEC 60601 covers requirements related to maximum permissible voltage, current, energy, power sources, needed insulation, testing of leakages, etc. In order to satisfy prescribed limitation of voltage, current or energy, means for reducing the risk due to electric shock in accordance with the requirements of standard IEC 60601-1 which can be divided in two categories:

- Means of patient protection (MOPP)—Means of protection for reducing the risk of electric shock to the patient.
- Means of operator protection (MOOP)—Means of protection for reducing the risk of electric shock to persons other than the patient.

Table 4 The classification of medical devices in the USA

Class I with exemptions	General controls for devices considered as low risks for human use
Class I without exemptions	
Class II with exemptions	Performance standards for devices considered as moderate risks for human use
Class II without exemptions	
Class III	Premarket approval for devices considered as high risks for human use

Standard also covers specific measurement tests of current leakage, insulation requirements, creepage distances and air clearances.

7 Conformity Assessment in Accordance with Requirements in the USA

The relevant legislation for the Medical Devices in the USA is under the responsibility of FDA[2] (U.S. Food & Drug Administration). Medical Devices are regulated by Medical Device Amendments of 1976 to the Federal Food Drug and Cosmetic Act.

The Medical Device Amendments of 1976 to the Federal Food, Drug, and Cosmetic Administration established three regulatory classes for medical devices. These three classes are based on the degree of control necessary to assure that the various types of devices are safe and effective [21]. FDA has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties referred to as panels.

The classification of medical devices in the USA is given in Table 4.

The USA has demands for marking of certain medical devices before their placement in the market, which must have Premarket Approval (PMA) equal to the European CE mark.

The most regulated devices are in Class III, as defined in the amendments as devices that support or sustain human life or are of substantial importance in preventing impairment of human health or presenting a potential, unreasonable risk of illness or injury. Insufficient information exists within Class III devices so that performance standards (Class II) or general controls (Class I) cannot provide reasonable assurance that the device is safe and effective for its intended use. Under Section 515 of the act, all devices placed into Class III are subject to premarket

[2]Medical Device Amendment—an amendment to the Food, Drug, and Cosmetic Act signed into law on May 28, 1976. The amendments gave FDA authority to regulate medical devices. FDA issues all approvals and regulatory required approvals depending on the class of the medical device [Marketing Clearance (510 K) or an Approval Letter (PMA)].

approval requirements. Premarket approval by FDA is the required process of scientific review to ensure the safety and effectiveness of Class III devices.

The official website of the FDA gives a wide range of information related to the medical devices which are useful for the manufacturer and other interested parties (user). Placing the medical device in the market of the USA consists of five steps [22]. Those steps are the following:

- Classify Your Device
- Select the Correct Premarket Submission
- Prepare the Appropriate Information for the Premarket Submission
- Send Your Premarket Submission to the FDA and Interact with FDA Staff during Review
- Complete Establishment Registration and Device Listing.

Premarket Notification 510(k)

Before marketing a device, each submitter must receive an order, in the form of a letter, from the FDA which finds the device to be substantially equivalent and states that the device can be marketed in the USA.

A 510(k) requires demonstration of substantial equivalence to another legally U. S. marketed device. Substantial equivalence means that the new device is at least as safe and effective as the predicate. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labelling, biocompatibility, standards, and other characteristics, as applicable.

The following four categories of parties must submit a 510(k) to the FDA:

- Domestic manufacturers introducing a device to the US market;
- Specification developers introducing a device to the US market;
- Re-packers or re-labellers who make labelling changes or whose operations significantly affect the device;
- Foreign manufacturers/ exporters or US representatives of foreign manufacturers/ exporters introducing a device to the US market.

510(k) is required for anyone who wants to sell a device in the USA after May 28, 1976 (effective date of the Medical Device Amendments to the Act), if the purpose is different from the intended use for a device which is already in commercial distribution and if there is a change or modification of a legally marketed device and that change could significantly affect its safety or effectiveness.

Third Party Review

The Accredited Persons Program was created by the FDA Modernization Act of 1997 (FDAMA), based on an FDA pilot. The purpose of the program is to improve the efficiency and timeliness of FDA's 510(k) process, the process by which most medical devices receive marketing clearance in the USA. Under the program, the FDA has accredited third parties (Accredited Persons) that are authorized to conduct the primary review of 510(k) for eligible devices. Persons who are required to submit 510(k) for these devices may elect to contract with an Accredited Person and

submit a 510(k) directly to the Accredited Person. The Accredited Person conducts the primary review of the 510(k), and forwards the review, recommendation, and the 510(k) to the FDA. By law, the FDA must issue a final determination within 30 days after receiving the recommendation of an Accredited Person. 510(k) submitters who do not wish to use an Accredited Person may submit their 510(k) directly to the FDA.

Once all described steps have been conducted, the medical device can be placed in the US market.

8 International Organisation for Health

At the international level there is a World Health Organization (WHO) established in 1948, (7th of April is celebrated as World Health Day). WHO represents a coordinating institution that is focused on international health within the United Nations. Under its domain, WHO realizes ensuring a leading role in the critical issues of health care and participation in partnerships where joint action is needed, preparing agendas and the transfer of knowledge, setting standards, promotes and supervises the implementation of standards, providing technical assistance in the construction of appropriate infrastructure, and controls the health status and evaluation of health trends. WHO publishes the International Health Regulations (IHR), that comprises a set of international rules structured to prevent and respond to acute public health risks, whether it is national, regional or international risk that have the potential to expand beyond the borders and threaten the health of people worldwide.

IHR represents international legal instrument that is binding for 196 countries around the world (including Bosnia and Herzegovina). In accordance with the third edition of the IHR's from 2005, which entered into force on June 15, 2007, the EC and its member states strongly support to the IHR and they will continuously support it in the future without any restrictions. IHR define the rights and obligations of countries to report public health events, and establish a number of procedures that WHO must follow in its work to uphold global public health security. Each country should have in place the infrastructure to monitor and measure the health risks with the aim to ensure the well-being of their citizens, and to prevent and control the epidemic outbreaks.

Also, on international level there is The Global Harmonization Task Force (GHTF) which was founded in 1993 by the governments and industry representatives of Australia, Canada, Japan, the European Union, and the United States of America to address the corresponding issues.

The purpose of the GHTF is to encourage a convergence in standards and regulatory practices related to the safety, performance and quality of medical devices. GHTF has done an overview of requirements for medical devices before placing it in the market by members of GHTF. From this overview it is possible to see the differences in approaches between the EU and the USA before placing the product in the market.

9 Medicine in the Field of Legal Metrology

Medical measurements are present in everyday life and they represent the basic process of prevention, diagnosis and treatment of diseases. In Europe there is an increased interest in the metrology decisions and conformity assessment decisions, which are of particular importance to carry out measurements in order to protect health.

Products with a measuring function must be designed and manufactured in such a way to provide sufficient accuracy and stability within appropriate limits of accuracy, taking into account the intention of the use of the product. The accuracy limits (permissible errors) are specified by the manufacturer himself. The measurements done by the device with a measuring function must be expressed in legal units of measurement in accordance with the provisions of Directive 80/181/EEC [23].

Metrology with its measurements is an integral part of our daily life. All measurements which are carried out with the purpose of any economic transactions, or measurements with which it's possible to take certain legal measures against or in someone's benefit, protection in the field of health and the environment, are to be classified as measurements of legal metrology. Individual governments proscribe regulations under legal metrology to meet its needs, except for the harmonized area which is equal and obligatory in all member states (11 measuring instruments, MID [24] and NAWI [25] Directive). One issue is common for all state economies and that is a fact that legal metrology is founded for the purpose of protection of the consumers (end users). OIML—International Organization of Legal Metrology has divided this category of metrology into four parts.

Those parts are:

- Legal Metrology and Trade
- Legal Metrology and Safety
- Legal Metrology and **Health**
- Legal Metrology and the Environment.

The accurate and precise measurements in the field of medicine allow easier diagnosis and identification of diseases on the basis of which it is possible to precisely determine the appropriate treatment of the patient, in order to help the patient in the best and safest way to receive effective treatment, but all through the usage of adequate medical instruments/ devices which fulfil the requirements described in the relevant legislation and standards.

In accordance with OIML D1 [26] document, governmental regulatory responsibilities include **health**, safety and environmental law. While these functions are disparate in nature, a common feature is that compliance with the law depends on measurement results. The scope of legal metrology may be different from country to country.

Therefore, the process of measurement is of direct concern to the government. Providing the laws and regulations, controlling measurement through market

supervision and developing and maintaining the infrastructure that can support the accuracy of these measurements (e.g. through traceability) is essential in fulfilling the role of government.

The scope of the legal metrology regulations (e.g. which types of measurements and measuring instruments or systems are subject to legal requirements) will depend on those markets that are important to the economy, on the categories of users that the government considers necessary to protect, and on the ability of the users to protecting themselves against abuse.

Since there are only 11 harmonized instruments, it is easy to conclude that the non-harmonized sector comprises of much higher number of instruments.

Non-harmonised sectors [27] are not subject to common EU rules and may come under the national rules. These sectors should still benefit from Treaty provisions governing free movement of goods according to Arts. 34–36 TFEU. National rules on these products are subject to a notification procedure that ensures they do not create undue barriers to trade.

In order to ensure the free movement of goods in non-harmonised sectors, the principals of mutual recognition, the 98/34 notification procedure and the application of Arts 34–36 TFEU are essential.

In some regions, due to the treaties or agreements, regional legislation may have precedence over national laws and regulations or may be recommended to national authorities. This is the case for example in the European Union, where European Regulations and European Directives are accorded higher status than national legislation.

Referring again to OIML Document D1 "Considerations for a Law on Metrology", the recommendation for government bodies building their metrology systems are encouraged to keep the following:

The priority is to set up the legal provisions related to the status of the bodies to which tasks will be allocated, and the financial provisions that will ensure their sustainability (national institutes, accreditation bodies), the general framework for legal metrological control and the first list of priorities for categories to be subjected to legal control, and the infringements, penalties and the powers of agents in charge of metrological supervision.

The scope of legal metrology that is the list of categories of measuring instruments must start with the most important categories for which the available resources allow the regulation to be correctly enforced. The scope can then be progressively extended as additional resources become available.

The obligations resulting from the OIML Treaty and from the WTO TBT Agreement (obligation to use OIML Recommendations as far as possible, and encouragement by the TBT Agreement to participate in OIML recognition and acceptance arrangements) should also be taken into account, as well as other obligations deriving from regional treaties or agreements.

Measuring instruments under legal metrology have to be regularly verified. Verification [28] of a measuring instrument represents conformity assessment procedure (other than type evaluation) which results in the affixing of a verification mark and/or issuing of a verification certificate.

As described in OIML Document D1 "Fields of use of measuring instruments subject to verification" Instruments, substances, and devices used in the diagnosis and treatment of humans and animals, in the manufacture of medicines, and in the monitoring of the medical environment (patient and hospital) should be considered for verification.

OIML has published a certain number of recommendations which indicate on verification procedures of medical devices. This will be described more in detail in the chapter dedicated to legal metrology. Medical devices covered by International Organization of Legal Metrology [27] are as follows:

- Sphygmomanometers, covered by OIML recommendation R 16-1 (from 2002)
- Medical syringes, covered by OIML recommendation R 26 (1978)
- Standard graduated pipettes for verification officers, covered by OIML recommendation R 40 (1981)
- Electroencephalographs—Metrological characteristics—Methods and equipment for verification, covered by OIML recommendation R 89 (1990)
- Electrocardiographs—Metrological characteristics—Methods and equipment for verification, covered by OIML recommendation R 90 (1990)
- Measuring instrumentation for human response to vibration, covered by OIML recommendation R 103 (1992)
- Pure-tone audiometers (including Annexes A to E), covered by OIML recommendation R 104 (1993)
- Clinical electrical thermometers for continuous measurement, covered by OIML recommendation R 114 (1995)
- Clinical electrical thermometers with maximum device, covered by OIML recommendation R 115 (1995)
- Equipment for speech audiometry, covered by OIML recommendation R 122 (1996).

OIML has covered only a part of medical devices with measuring function; however the number of medical devices in use is much higher. For medical devices that are applied in the EU but which are not covered by legal metrology in some countries calibration process has to be ensured with an adequate traceability chain. Requirements for harmonizing a large number of medical devices in legal metrology are constantly increasing.

One of the countries, namely Bosnia and Herzegovina, which is not a member of the EU, but it regularly takes part in WELMEC[3] (European Cooperation in Legal Metrology) activities and OIML activities has extended the list of medical devices in the field of legal metrology in accordance with its national needs.

Medical instruments with measuring function, which are part of the Legal metrology system in B&H, are as follows:

- Defibrillator,
- Infusomats and perfusors,

[3] http://www.welmec.org/.

- Patient monitors,
- Neonatal and paediatric incubators,
- Respirators,
- Anaesthesiology machines,
- Therapeutic ultrasound devices,
- Dialysis machines,
- Electrocardiographs ECG/EKG.

This action proved to be very successful, according to the feedback from the legal entities responsible for performing verification in this subjected field. The majority of devices tested have shown certain non-conformities related to the requirements prescribed in legal documents and/or by the manufacturer [29–33].

Unlike other measuring instruments covered by legal metrology, many of the medical devices need to be traceable to one measuring standard which is not fully developed yet. The future of development in this field of metrology lies in facilitating the process of calibration, i.e. establishment of a traceability chain via a single measuring standard for a certain type of medical device.

Turkey has also already recognised importance of metrology in medicine and has initiated via Turkish Institute of Metrology (UME) [34] a study on appropriate traceability of medical devices. The aim of the study is to develop a five year roadmap and a plan for providing reliability and metrological traceability in medical measurements. To get closer to intended aim, UME has established a Medical metrology research laboratory.

Certain measuring instruments used in medical purposes are also recognised in the Portuguese legislation [35]. The Institute of Metrology of Portugal dealt also with the question on how to improve metrological traceability of medical instruments.

Comparing the current situation of those countries dealing with medical instruments in a controlled area it is obvious that the main issue in general refers on how to ensure or improve adequate metrological traceability.

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