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OVERVIEW PROFESSIONAL PAPER

The role of metrology in healthcare and the new regulatory framework for Medical Devices

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Abstract.

In order to be placed on the market, a medical device must comply with the EU Medical Devices current legislation. Reliable and accurate measurements and continuous monitoring of medical devices are the key to diagnosing the patient condition quickly and taking an appropriate action. Medical Device Directives and Regulations ensure that the product placed on the market is safe and it performs its intention of use.
The focus of the paper is on the role of metrology in healthcare and on the new regulatory framework for medical devices. The new Medical Device Regulation (MDR) is replacing the current directives to establish a modernized legislative framework for medical devices. The technical requirements regarding the former and the new legislation are presented.

Keywords: medical device, blood pressure monitors, metrology, medical device regulation, conformity assessment, safety

Vloga meroslovja na področju zdravstva in nov regulativni okvir za medicinske pripomočke

Za dajanje na trg mora biti medicinski pripomoček v skladu z veljavno zakonodajo EU o medicinskih pripomočkih. Zanesljive, natančne meritve in stalno spremljanje medicinskih pripomočkov so ključnega pomena za hitro diagnosticiranje stanja in ustrezno ukrepanje. Direktive in uredbe o medicinskih pripomočkih zagotavljajo, da je izdelek, ki je dan na trg, varen in da izpolnjuje svoj namen uporabe.
V prispevku se osredotočamo na vlogo meroslovja na področju zdravstva in na nov regulativni okvir za medicinske pripomočke. Nova uredba o medicinskih pripomočkih (MDR) nadomešča sedanje direktive, ki vzpostavljajo posodobljen zakonodajni okvir za medicinske pripomočke. Predstavljene bodo tehniške zahteve stare in nove zakonodaje.

1 INTRODUCTION

Medical devices are of an extreme importance for diagnosing and treatment of diseases.

To ensure a proper diagnosis or treatment, the devices shall comply with the applicable technical requirements. The malfunctioning might considerably affect the patient's safety. Therefore, it has to be ensured that medical devices before being placed on the market comply with regulatory requirements. Many patients to suffer from consequences or even death due to the failures and defects of medical devices. Therefore, a continuous monitoring and verification of medical devices are mandatory. As an example, an incorrect blood-pressure measurement can lead to an incorrect diagnosis and inadequate treatment. This indicates that the metrological control has a very important role in the patient's diagnosing.

In May 2021, the EU legislation for MD (medical devices) has faced significant changes.[1]

The Directive 90/385/EEC (for active implants) and Directive 93/42/EEC (for other medical devices) enforced in 1990 to regulate medical devices placed on the European Union (EU) market where in 2017 replaced by the EU 2017/745 and 2017/746 regulation. Due to the COVID-19 outbreak, the EU 2020/561 regulation that replaced the EU 2017/745 regulation came into force on May 26, 2021.

The new regulation (MDR) includes a modernized legislative framework for medical devices. Its aim is to improve the quality of medical devices, particularly the high-risk devices, by improving the post-market surveillance and the transparency of their use based on an all-inclusive EU database of medical devices.

2 ROLE OF METROLOGY IN THE FIELD OF MEDICAL DEVICES

Metrology and standardization are the key components ensuring traceability of medical devices.[2]

Metrology in medicine is a necessity in order to define directives, regulations and standards applicable for inspection of medical devices. Manufacturers have to

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follow the relevant legislation in order to increase safety in the production of their medical devices.

A laboratory that aims to inspect medical devices should be accredited according to the ISO 17020 standard [3]. It should calibrate its working standards in a laboratory accredited according to the ISO/IEC 17025 standard. Therefore, the traceability chain ensures that the measurements performed with medical devices are traceable, reliable, accurate and comparable at different locations over time. [4] To demonstrate compliance with the metrological traceability chain, measuring instruments should have their calibration or verification certificates.

There is a variety of medical measurements and their importance in prevention, diagnosis and treatment of diseases is considerable. An appropriate diagnosis and treatment relies on the accuracy and proper functionality of medical devices that directly affects the patient's health.

Such example is a metrological control of non-invasive blood-pressure monitors. In Europe, almost half of the population suffers from hypertension, which is the cause of more than 10% of all non-accidental deaths [5]. Hypertension requires monitoring the blood pressure on a regular basis and appropriate treatment. A high blood pressure can lead to serious medical conditions, such as heart attack, stroke and kidney failure. Early detection and treatment of hypotension or hypertension will help to reduce the risk of development of these conditions. Reliable and accurate blood pressure measurements taken with reliable and metrologically controlled blood pressure monitors are therefore essential for the diagnosis of hypertension. Recent studies show that the error of a blood pressure monitor is on the level of ±5 mmHg, which is the permissible limit at which a blood pressure monitor over- or underestimates the true blood pressure compliably with the IEC 80601-2-30 standard, then over 65 million Europeans would be affected either by untreated hypertension or by the side effects of unnecessary treatment [6]. An incorrect blood pressure measurement can lead to an incorrect diagnosis and treatment and therefore represents a major health risk for some diseases. This example shows that metrological control is of a vital importance in the blood-pressure diagnosis of a patient. Devices that are not validated and periodically inspected should not be marketed and used. Many barriers have been identified for accurate blood pressure measurements including limited awareness, lack of training of health providers and difficulty in the device maintenance [7].

A proper working of medical devices is not only ensured by being inspected medical devices but also by being submitted to a regular preventive maintenance program.

3 MEDICAL DEVICE LEGISLATION

The EU legislation takes a form of directives and regulations followed by appropriate harmonized standards. Medical devices should be given Conformité Européenne (CE) marking before being placed on the market. This allows manufacturers to work with the notified body (NB) to confirm the conformity of their devices. The mark is affixed in the product after the manufacturer has signed the declaration of conformity [1].

It is important that regulations and their amendments that may affect the product CE marking are followed in order to assure that only the reliable and safe medical devices are placed in the European market compliably with the EU legislation.

3.1 Harmonized Standards

Through the harmonized standards, the manufacturers of products ensure that their products meet the set requirements. However, when a manufacturer applies some other standards he should prove that the applied standard is an equivalent and the product safety and performance should be demonstrated. By following the imposed standards, both the manufacturer and the consumer are protected. If in the opposite case, the free movement of goods would be restricted, and barriers to the trade would give rise to higher costs and difficulties in placing product on the market.

To minimize the boundaries and facilitate trade of medical devices, national standards should be harmonized with various international standards published worldwide by organizations such as ISO and IEC. One of such standard is the ISO 13485 standard which specifies requirements for a quality management system for manufacturers of medical devices.

The ISO 13485 standard specifies provisions for medical devices organizations and manufacturers to demonstrate that they provide products or devices that meet regulatory requirements as well as satisfy customer requests.

The International Organization of Legal Metrology (OIML) is an intergovernmental treaty organization, which issues recommendations for different measuring devices including medical devices,[4]. In February 2021, they published two recommendations for blood pressure meters, namely OIML R 148:2020 and OIML R 149:2020 superseding OIML R 16:2002. In their recommendations, the maximal permissible error (MPE) for the cuff pressure is set at ±0.4 kPa (±3 mmHg) or ± 2% of the reading. OIML R 148:2020 and OIML R 149:2020 also define MPE as determined by clinical investigations for ±0.7kPa (±5 mmHg) and the maximum standard deviation of 1.1 kPa (8 mmHg).

4 THE NEW EU REGULATORY FRAMEWORK FOR MEDICAL DEVICES IN THE EUROPEAN UNION

4.1 Conformity Assessment of Medical Devices

Manufacturers have to perform conformity assessment of their products in order to demonstrate that the applicable requirements for a product have been met. The overall objective of the conformity assessment procedure is to make sure that all legislative requirements are met before the product is placed on the market.

Conformity assessment route is different for different classes of medical devices.

Before placing the product on the market, the manufacturer determines the class of its device and then decides for the most suitable conformity route to follow. Medical devices are categorized in three different classes that have different conformity assessment procedures:

- Class I – low risk medical devices
- Class IIa – higher-level risk medical devices
- Class IIb – high-level risk medical devices
- Class III – highest-level risk medical devices

Since the Class I devices show a low-level risk, the conformity assessment procedures for these devices can be carried out under the responsibility of the manufacturers.

The Class IIa devices show a higher-level risk and therefore a NB should be involved.
The Classes IIb and III devices are the devices with the highest risk level, therefore inspection by a NB is required.

The manufacturer can select different options of conformity assessment routes to meet the requirements of the medical device regulation (MDR) to place a device on the market. Depending on the device class and consequently on the risk level of medical devices, different procedures of the conformity assessment in accordance with the MDR Annexes can be applied. Annexes to be applied depending on the device risk class of the device are given in Table 1.

Before placing the device on the market as compliably with MDR, the manufacturer has to affix the CE mark according to Annex V and provide the declaration of conformity according to Annex IV.

Being CE-marked proves that the device achieves the performance intended by the manufacturer [9].

There are eight modules (labelled with letters from A to H) which can be combined in a variety of ways to perform the conformity assessment procedures [5]. They specify the responsibilities of the manufacturer and the involvement of the in-house accredited or notified conformity assessment body. NBs are designated bodies by the Member States which have to ensure that the conformity assessment procedures are done according to the MDR requirements [9].

Table 1: Conformity assessment routes for medical devices

Annex IX	QMS and technical documentation. It is used when a full QMS is implemented by the manufacturer.
Annex X	EC-type examination
Annex XI	Product conformity verification. This annex is composed of the A and B: A - Product Quality Assurance and B - Product Verification

An NBs assessment consists of:

- Assessment of technical documentation,
- Conformity assessment,
- Issuing of certificate of conformity and
- Regular surveillance audits.

The conformity assessment bodies that perform conformity assessment activities should be accredited by the national accreditation body for a particular standard that they are performing their activity. Through accreditation they assure their competences to perform a conformity assessment for their specific task [10].

The New Approach Notified and Designated Organizations (NANDO) database consist of the registered NBs [11]. Through the NANDO database the manufacturers can check NBs and choose from the database who can assess the conformity of their product. If the manufacturer fulfils all the requirements, and NB is satisfied with the manufacturer the manufacturer is then allowed to use the CE Marking. Once the product bears the CE Marking and is registered on the database, it can circulate freely in Europe and countries that have mutual agreements with Europe.

4.1.1 Conformity assessment for the Class I devices

Medical devices of the class I show a low risk.
The only conformity route for the Class I medical devices is to prepare the technical documents in accordance with the MDR Annex II and Annex III. For the Class I medical devices including sterile products (Isp), with a measuring function (Imf) or reusable surgical instruments (Irs) manufacturers will need to have a quality management system to control the production set up according to Annex XI Part A or to control specific characteristics according to Annex IX, Chapter I. For sterile, measuring function products or reusable surgical Class I instruments NB will be implicated to control their Quality Management System (QMS). The conformity assessment

route for the Class I and Class Isp, Imf and Irs is shown in Figure 1[12].

4.1.2 Conformity assessment for the Class IIa devices

Medical devices of the Class IIa are the devices that show a low to a medium risk. Such devices are: ultrasonic diagnostic devices, blood pressure monitors etc.

For the devices that are part of the Class IIa or Class IIb non-implantable devices, the conformity assessment procedure can be done through Annex IX - The Review of Full QMS.

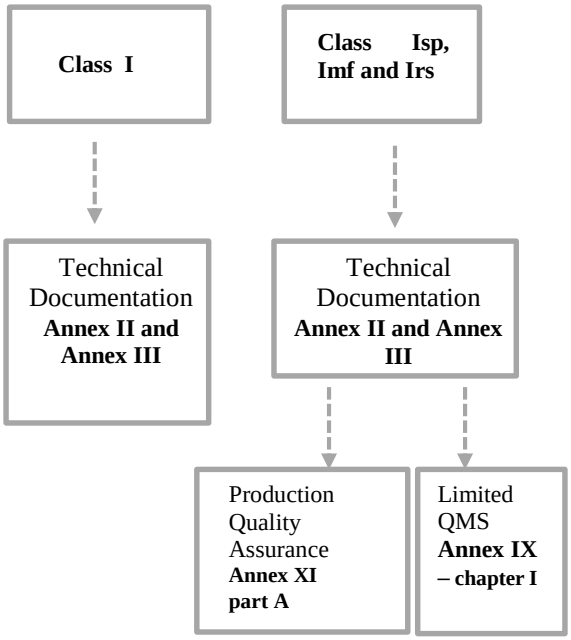

Figure 1. Conformity Assessment of the Class I medical devices.

There are two possibilities for manufacturers as shown in Figure 2. They can choose between the conformity assessment procedure based on Annex IX by reviewing their full QMS or by building technical documentation based on Annex II and III and selecting a route of conformity based on production control according to Annex XI, Annex XI - Section 10 Production Quality Assurance or Annex XI - Section 18 Product Verification.

The conformity assessment route for the Class IIa is shown in Figure 2 [12].

4.1.3 Conformity assessment for the Class IIb devices

The Class IIb medical devices are the devices that show a medium to a high risk. Such devices are defibrillators, pulse oximeters, incubators for babies, etc.

Manufacturers of these devices can choose two different conformity routes as shown in Table 4. They can choose to follow QMS given in Annex IX (MDR Chapter I, Section 4). Alternatively, they can choose the conformity route shown in Annex X (Type-Examination) and provide an assessment according to Annex XI (Product Conformity Verification - Part A or part B). The conformity assessment route for the Class IIb devices is given in Figure 3 [12].

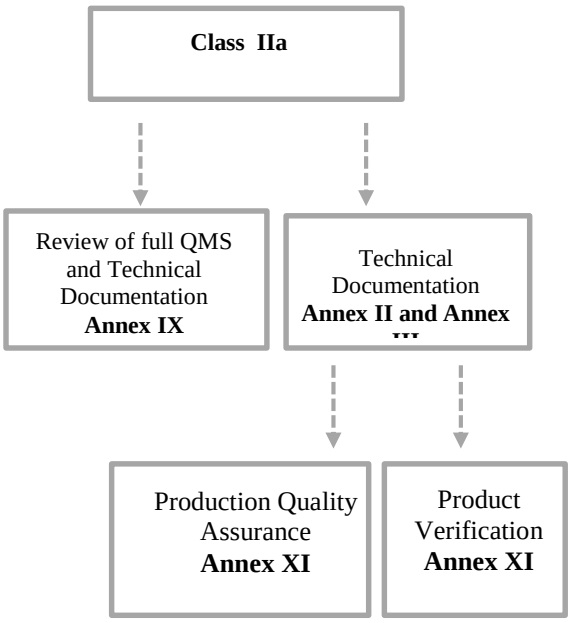

Figure 2. Conformity Assessment of the Class IIa medical devices.

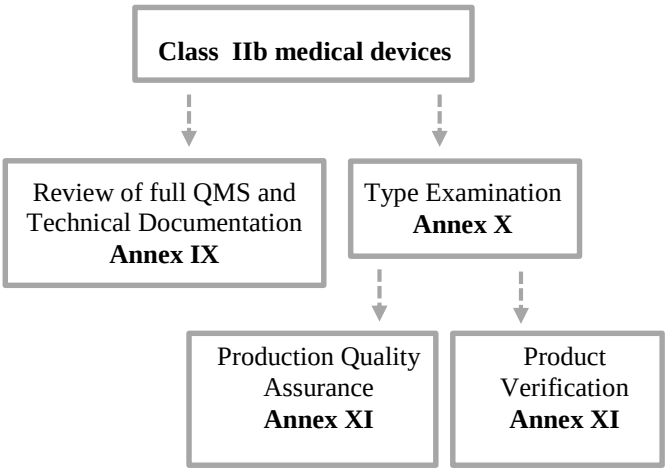

Figure 3. Conformity assessment for the Class IIb mededical devices.

4.1.4 Conformity assessment of the Class III medical devices

The Class III medical devices are the devices that show a high risk. Such devices are heart valves, pacemakers, etc. The conformity assessment procedure for the Class III medical devices is very similar to the conformity assessment procedure of the Class IIb medical devices. The manufacturer can choose to follow the full QMS

given in Annex IX (MDR Chapter I, Section 4) and full technical documentation review.

Alternatively, the manufacturer can choose the conformity route described in Annex X (Type-Examination) followed by an assessment given in Annex XI of the Product Conformity Verification, Part A (Production Quality Assurance Route) or part B (Product Verification Route). Figure 4 shows the Conformity assessment route for the Class III medical.[12].

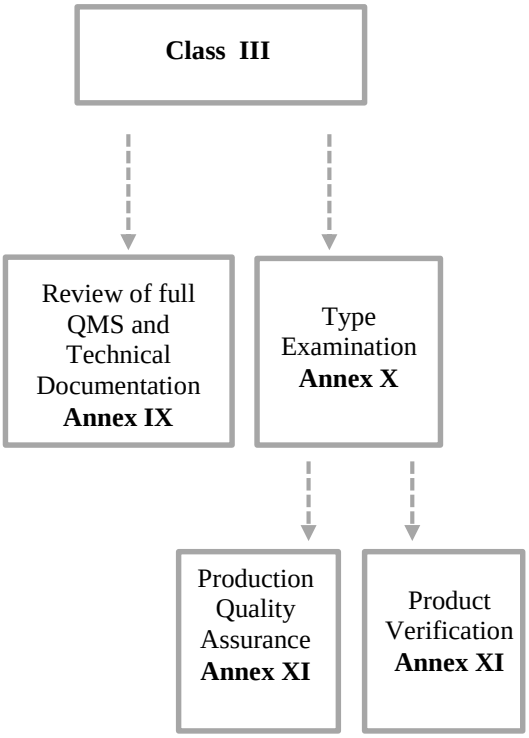

Figure 4. Conformity Assessment of the Class III medical devices.

4.2 Conformity Assessment of blood-pressure monitors

This section provides a comprehensive description of the conformity assessment procedure of medical devices set up according to the new MDR requirements. The Figure 5 shows the conformity assessment procedure to be followed prior to placing blood pressure monitors on the market. A manufacturer can follow it by implementing the full QMS, Annex IX or with Production control, Annex XI. This means that the manufacturer chooses either module H or module A and one of the modules F1, D1 and E1 modules [13].

NB assesses and monitors the QMS compliability with H1, compliability with module A, EC Declaration of conformity, the manufacturer prepares the technical documentation and chooses one of the below options:

Module F1 - EC Verification or
Module D1- Production Quality Assurance or
Module E1 - Product Quality Assurance.

This means that NB assesses every device compliability with the Module F1 (non-sterile products) and performs the production quality assurance audit compliability with the Module D1 and the product quality assurance (for non-sterile products) complibability with the Module E1. Since blood pressure monitors are classified as the Class IIa devices NB reviews the technical documentation for a minimal number of representative devices of each category.

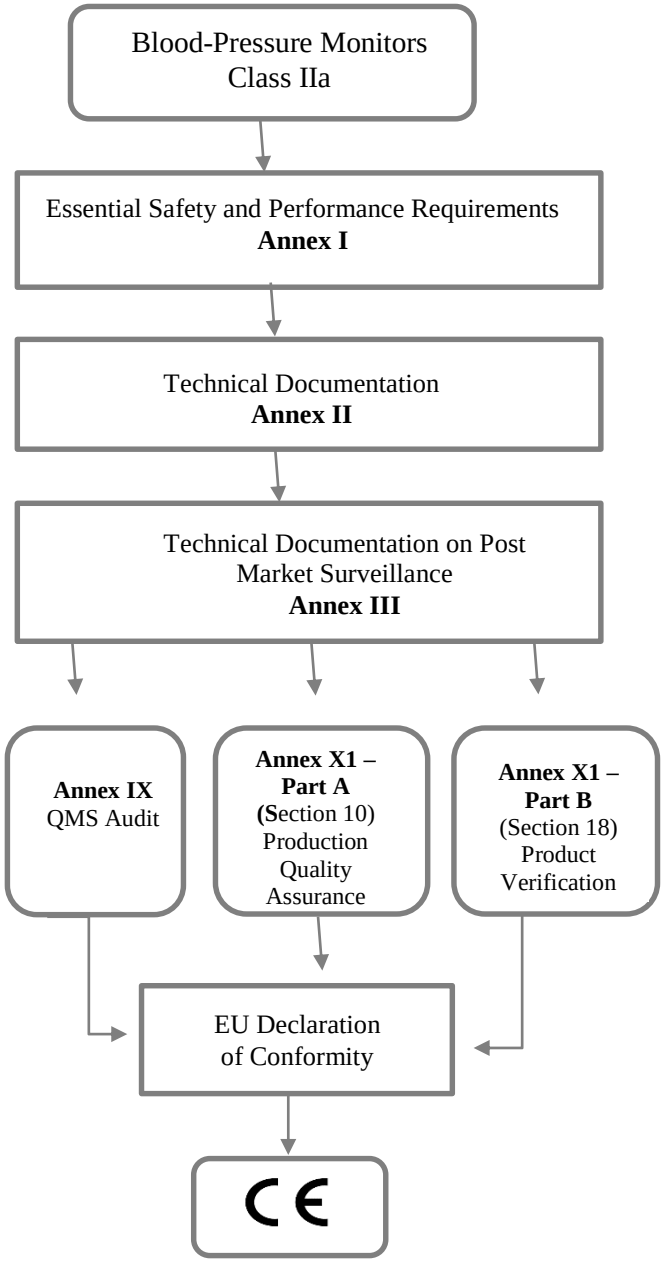

Figure 5. Conformity Assessment Route for blood-pressure monitors.

According to the risk degree, blood pressure monitors are classified as the Class IIa devices. These medical devices should be manufactured compliantly with the QMS to assure a continuous quality and fits the company.

Medical devices manufacturers are recommended to comply with the requirements for a Quality Management System given in the ISO 13485 standard. They then prepare a declaration of conformity to prove that device complies with MDR. They choose NB to audit them according to ISO 13485 standard. NB reviews the manufacturer's technical documentation for blood-pressure monitors and decides to grand or not the EC certificate. The manufacturers are responsible for meeting the legal requirements for their devices, and NB assesses weather they meet the directive requirements.

It is important that during the time the medical devices are traded, manufacturers reassess them, to detect any possible problem or failure. The customer's feedbacks and complaints can help them to improve their products. Detection of non-conformities is then followed by corrective actions that may prolong their devices market life cycle.

4.3 MDR advantages compared to the MD Directive

4.3.1 Post market surveillance

MDR foresees a more rigorous post-market surveillance by NBs. This particularly involves the high-risk devices in order to reduce the risk of their unsafe use and to ensure that only safe devices are traded. For this purpose, unannounced visits and regular device checks are made to avoid risks.

4.3.2 Expanded scope of medical devices

The scope of the MDR medical devices and active implantable medical devices is expanded, as some of the products that the MDD treated accessories are now treated as devices. As an example are products used for cleaning, disinfecting or sterilizing medical devices that were previously considered accessories are now considered devices. Another example are collored contact lenses and cosmetic implant devices as well as the devices used for "prediction and prognosis" of a disease.

4.3.3 Applying the unique device identification (UDI)

Another MDR requirement is identification of medical devices using UDI which enables tracing medical devices, simplifies their traceability, improves monitoring by competent authorities and bans falsified medical devices. This altogether reduces the possible medical errors.

The UDI number includes numbers and letters and is placed by the manufacturer on the MD packaging prior to being place he market. The UDI number is defined according to a coding standard.

The European Databank on Medical Devices (EUDAMED) is an IT system developed by the EU Commission for the implementation of the 2017/745 and 2017/746 Regulations. The designation of companies is authorized by the EU Commission in order to provide the UDI-DI number.

UDI is a number that identifies a specific product. UDI on a product consists of two parts: UDI-DI and UDI-PI. UDI-DI, which is static number, identifies a specific device. It is referred to technical documentation, certificates and declaration of conformity.

The MDR term "Basic UDI-DI" which is used for a group of medical devices with the same characteristics is used for administrative purposes.[14] The basic UDI-DI dos not need to appear on the device packing.

4.3.4 Clinical evidence for medical devices

According to MDR, manufacturers will have to consider the changes and the need for clinical evaluation as well as circumstances under which clinical evaluation cannot be made.

Manufacturers will have to prove with enough clinical evidences that their medical devices are safe and that they perform correctly [15].

If required they will have to conduct further clinical investigations. The amount of clinical evidences should be made accordingly to the characteristic and class of the device.

According to MDR, clinical investigation should be done for the Class III and implantable devices. Some of the exceptions are the devices that are almost the same as the ones that were traded before by the same manufacturer or to be traded as an equivalent of a device manufactured by some other manufacturer.

In addition, MDR will engage independent experts to provide an opinion to NB on specific high-risk products before they are certified.

5 CONCLUSION

The paper highlights the importance of metrology and measurements and the importance of continuous monitoring and verification of medical devices. To assure proper diagnostics and treatment of patients, the measurements shall be utmost accurate.

Blood-pressure monitors measure one of the most important vital signs, therefore they should be monitored and inspected regularly as recommended by the manufacturer.

The paper discusses the implementation of the MDR specifications for placing on the market and the conformity assessment route foreseen for the blood-pressure monitors according to the conformity assessment routes for the Class IIa medical devices. Blood pressure meters will bear the CE marking when placed on the market, thus proving that they are safe for their intended use.

This paper agrees that the newly adopted MDR offers a modernized legislative framework for medical devices and opens a space for further improvements.

To comply with the new requirements, manufacturers shall have to take certain adaptation steps.

To improve the quality of their products the high-risk devices should be well checked, they should be post-market monitored and their transparency enabled based on an all-inclusive medical device EU database.

Patients and manufacturers will benefit from the MDR implementation. The manufacturers will be able to develop innovative and improved-safety medical devices enabling their higher transparency and traceability. To comply with MDR, manufacturers will be faced with many new challenges in terms of the cost of the MDR implementation.

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