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A futuristic study on in-vitro medical devices regulations

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ABSTRACT

The In-Vitro Medical Devices Directive (IVDD) established in 1998 by the European Union met the requirements of the single medical device market. In the due course, IVDD could not regulate all new technical and medical developments in the sector. The IVDD 98/79/EC, was preceded with IVDR 2017//746; which defined and demonstrated conformity to essential requirements, established harmonized standards and facilitated the organization of 'Notified Body' (NB), Competent Authority oversight and market surveillance. IVDR implemented streamlines as defined in Annex I of the EU IVDR 2017/746 conforming to the relationships between the performance requirements and general safety, and Annex I of the EU Directive 98/79/EC for IVDD for the essential requirements. The importance of the Unique Device Identification and its implementation in the safety and conformity of the device was made stringent for the manufacturers. The recent developments in IVDR, with reference to EUDAMED database, enable the applicant for accessing of data entered for the revival, correction and the assessing of information.

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INTRODUCTION

In Europe, the safety regarding health and population regarding IVDs is the responsibility of European Union (EU). In order to maintain this, regulation was applied to all the IVDs marketed in Europe irrespective of where they were manufactured. The council on IVDs was formed in 1998 named as Directive 98/79/EC which met the requirement of the single market device for IVDs. In 2008 and 2010, the deficiencies of the IVDD were identified by the council, update was initiated. Common features of risk identification, conformity assessment protocols and clinical evidence continued to exist. (In vitro medical device regulation overview , 2017). The introduction of genetic testing, companion diagnostic device, risk-based classification system of the IVDs were proposed to the European commission. In 2012, the initial suggestion for the regulation of medical device and IVDs were made. In 2014, 254 amendments proposed for the IVDR (Factsheet for Manufacturers of in vitro Diagnostic Medical Devices, 2017). In 2015, the council responded for the proposal and finally on 5^{th} May 2017 the regulation was published officially. A changeover period of 5 years was set to the manufactures to follow this regulation.

Genetic testing

Introduced as to the predisposition to a medical condition or disease, there are already guidelines in the IVDD that they will now officially be known as IVDs for their screening.

Devices for point of care testing

Designed to be examined by a health professional outside of a laboratory environment, usually near to

or on the side of the patient. It is exempt from self-testing.

Companion diagnostic

A corresponding medical substance important to a device's safe and effective use (to identify potential consumer/s, identify patients likely to experience adverse reactions).

Single-use device

Suggested to be used in a single process. The single-use system idea has already been introduced in the MDD, but for IVDs it is new. This particular condition only affects the device's user information and registration, as this information must be specified on the tag, in the Use Data information and in the UDI registration information for the IVD (SA Health , 2020).

Falsified device

A device displaying a false identity is a falsified device, an origin device and/or a CE labelling certificate (Europe In Vitro Diagnostic Devices Regulation (IVDR) CE Marking Regulatory Process, 2019). Nevertheless, the scope of this definition does not include unintended non-compliance or infringements of intellectual property. The specific status of the item is significant because it obliges suppliers and importers to report forgeries and allows authorities to take appropriate actions.

Kit

A collection of components packaged together for the purpose of conducting a particular test or part of it.

IVDR risk classification

The new classification of the IVDs is showed in the Table 1. (In vitro medical device regulation overview , 2017).

The new classification scheme means that IVD devices not fitting into any of the classes will be considered Class B, falling under notified body supervision (In vitro medical device regulation overview , 2017).

1. The class A devices are self-declared conformity and sterile; class A devices are intervened by the notified bodies.
2. The class B devices are intervened by the notified bodies by QMS or by review of the technical documents.
3. The class C devices are intervened by the notified bodies by the QMS audit, production quality assurance and the technical document.
4. The class D devices are intervened by the notified bodies by the QMS audit, batch verification, production quality assurance and assessment of technical documents (In vitro medical device regulation overview , 2017).

In Vitro Diagnostics Device Regulation (IVDR)

Newly initiated requirements to the IVDR are compared to the IVDD; the important changes are briefed.

General requirements

1. Manufacturers to implement, create, report and maintain a system of risk management. Risk management is a continuous process throughout a device's entire lifecycle that requires a regular system update.
2. A risk management plan for each product is developed by the manufacturer.
3. Identify and evaluate predictable device-related hazards.
4. Provide users with appropriate training for safety information, i.e. (warnings, precautions and contraindications).
5. Elimination of user-related risks.
6. The manufacture reduces the risk associated with the ergonomic function of the product. Technical awareness, training, experience and atmosphere are given priority where users' health and physical conditions are noted.
7. All possible risks are planned to be reduced and appropriate, taking into account the potential benefits of the patient.

Performance characteristics

1. The device's quality characteristics shall be retained as defined by the device.
2. During the use of the system, the characteristics and output of the device will be precisely controlled;
3. Self-testing device performance obtained by layperson.
4. Near-patient monitoring quality tool is accessed in the appropriate environment (Medical Device Control Division, 2020).

Physical and biological chemical characteristics

Table 1: Classification of In vitro diagnostics

Medical Device Class	Level of Risk
Class of device A	Low Risk of an Individual
Class of device B	Moderate Risk of an Individual
Class of device C	Medium Risk of an Individual
Class of device D	High Risk of an Individual

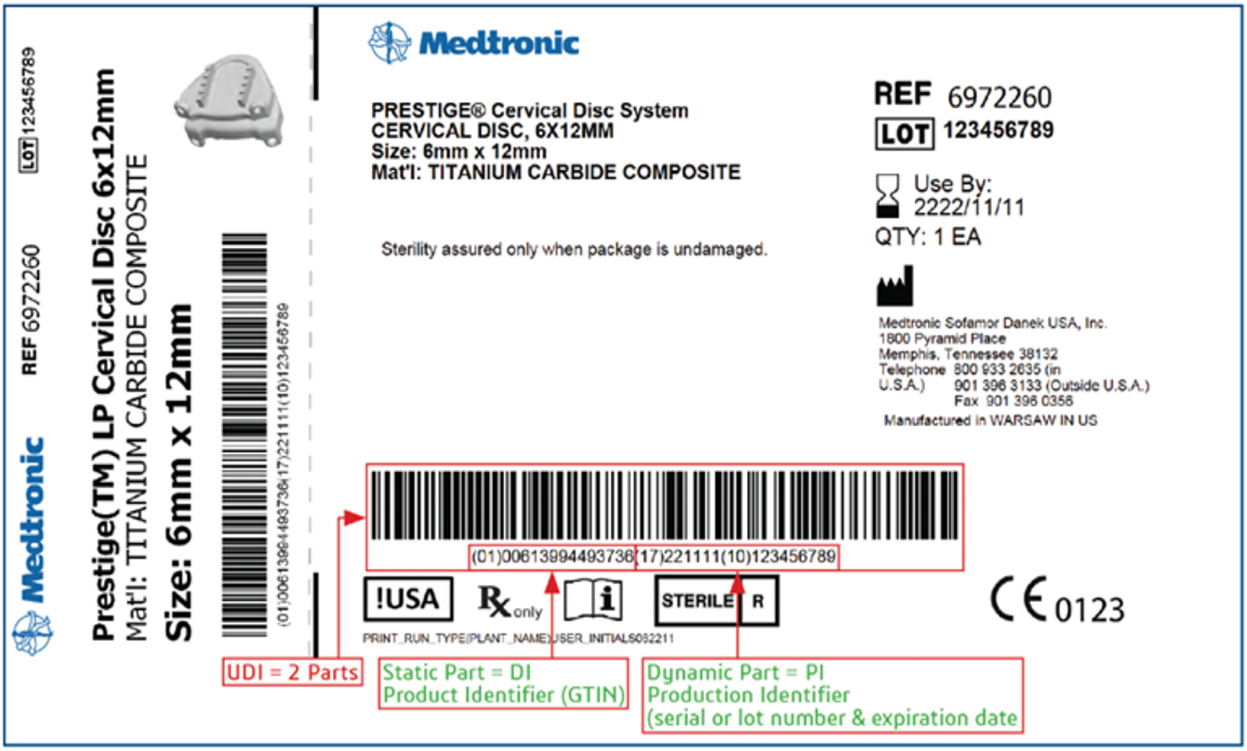

Figure 1: UDI labelling of an In-Vitro Diagnostic

1. The device intends to be manufactured in such a way that the risk caused by the substances that are released from the debris etc. special care is given to carcinogenic substances which can cause solemn health issue to the human.
2. The device shall be manufactured in such a way that the entry of particulate matter is avoided even from the environment it is proposed to be used (Europe In Vitro Diagnostic Devices Regulation (IVDR) CE Marking Regulatory Process, 2019).

Infection and microbial contamination

1. The labelling distinguishes between identical or similar products put on the market in both sterile and non-sterile state plus the use of a sign to denote sterile devices.

Construction of device and interaction with environment

1. The risks associated with the potential negative interaction of the software with the IT environment in which it operates and communicates.
2. Risk in the unit for unintended particulate matter.
3. Risk of incorrect identification of specimen or numeric number due to incorrect information etc.
4. Foreseeable risk interference with another device.
5. Adjustment, calibration, and maintenance must be kept in mind while manufacturing the device that can be done result in safe and effective use.
6. Devices intended to be used in combination with other devices or services shall be designed and manufactured to be reliable and safe.

Electronic programming system

1. The software is intended to be produced and manufactured in accordance with the principles of design life cycle, risk management, including information security, testing and validation, for devices that are embedded in software or software.

2. Manufacturers shall lay down the minimum hardware, IT network and IT security requirements, including protection from unauthorized access, necessary to run the program as intended.

Device equipped with energy source

1. The single fault conditions of the device intend to be adopted to eradicate the consequent risk as far as possible.

2. Devices shall be designed and manufactured to provide an intrinsic immunity level to electromagnetic interference that is sufficient to allow them to operate as intended.

Protection against mechanical and thermal risk

Errors that occur when fitting or refitting those parts that could be a source of risk are made impossible by designing and building certain parts or, failing that, by providing information on the parts themselves and/or their housing. Similar information shall be given on moving parts and/or their housing where it is necessary to know the direction of movement to avoid a danger.

Labelling and instructions for use

1. Labels are meant to be made available in a human-readable format and may be complemented by machine-readable data such as radio frequency identification or bar codes.

2. When the product is used by clinicians, the marking shall be in the non-paper electronic format, unless the device is intended for near-patient research.

3. The information supplied by the manufacture must give details about limitations, contra-indications, precautions or warning

4. Unique device identification (UDI) should be attached to each device.

5. The date of production must be included in the lot number or serial number so long as the date is clearly identifiable.

6. Correct documentation should be made available on the respective system websites if the instructions for use are not in paper form.

7. An indicator of that fact if the system is intended for single use. A single use warning from a supplier shall be included.

8. Self-testing device tag shall contain the following,

a). Specimen form required for the experiment to be carried out.

b). Need for additional material for test.

c). Further assistance and advice details.

Sterile packaging

1. An indication that the sterile packaging is known as

2. A declaration that the product is in a sterile state.

3. Sterilization process.

4. Manufacturer's name and address.

5. Device overview.

6. Manufacturing month and year.

7. Device time limit for use.

8. Instructions for testing the application instructions.

Information on instructions to use

1. The intended purpose of the device shall provide sufficient information to allow the user to understand the clinical context and to enable the intended user to interpret the results correctly.

2. For devices that consolidate electronic programmable frameworks, including programming, or programming that are devices in themselves, least basics concerning equipment, IT systems attributes and IT safety efforts, including security against unapproved get to, important to run the product as planned

3. Preparation of reagents, selection and/or preparation of samples and information on how to carry out the experiment and analysis of the findings for the experiments to be carried out.

4. Information on substances that interfere with or impair the output of the system.
5. It is essential to provide warnings or precautions for the safer disposal of the device or its accessories.
6. Infection or microbial hazards such as consumables contaminated with potentially infectious materials of human origin should be included in this data.
7. Batteries or materials emitting potentially hazardous radiation levels resulting in environmental hazards.
8. Explosion of physical hazards.
9. A notice to the consumer that any serious incident involving the device shall be reported to the manufacturer and to the competent authority of the Member State in which the user and/or the patient are registered.
10. Specifications for specific equipment such as a clean room setting or special training such as radiation safety or the expected user's qualifications.

Unique Device Identification (UDI)

It is a number representing a particular product. There are two elements of the UDI

1. UDI-DI (Device Identifier)
2. UDI-PI (Product Identifier)

The UDI-DI is the identifier of the unit. It recognizes a specific portfolio device. This is the UDI number static part. Within the same meticulous product, it doesn't change. In a specific presentation of the same device, the UDI-DI is linked to a specific device (In vitro medical device regulation overview, 2017). Figure 1 shows the different labeling of the UDIs in the IVDs.

UDI-PI is the identification of the 'production'. It's the UDI's dynamic part. It provides information on lot number, serial number, date of manufacture, date of expiry. The UDI-PI is important for identification of a specific batch of products affected by a production error. The manufacturer must select and control his suppliers because all devices carrying the same UDI-PI must have identical batches of raw materials and components to manage the UDI-PI appropriately (IMDRF, 2019).

UDI is the declaration of conformity, certification, label/s and for identification during distribution, use, incidents and field safety corrective actions. This new system of the UDI will lead to unambiguous device identification and easy, direct access to the information. UDI will be the code that identifies the dataset in EUDAMED.

The agencies that are responsible for the issuing of the UDI number is chosen by the European commission. The only company that is issuing the UDI number to the medical device is the "Informationsstelle Fur Azeispezialitaten" (IFA GmbH). This is a German company; other agencies responsible are GS1 ASBL, HIBCC and ICCBBA which are already existing agencies for US-FDA.

Once the UDI is generated, each UDI code must be applied in both human and machine-readable form by the authorized agencies. From the unit of use to the highest package level, the UDI code should be presented at each applicable packaging level. According to the level of packing, the device must have its own DI (GTIN) for the trade. "Direct marking" is required for devices, which are intended to be reused or reprocessed. Proper determination must be made whether their products fall under Direct Marking criteria or whether their products meet an existing exception (IMDRF, 2019).

Class I and IIa single-use devices packaged and individually labelled in the EU

The barcode can be applied to the next higher packaging containing several individually packaged devices. This does not apply if the health care provider has no access to the higher level of device packaging (e.g. home care devices).

'Direct marking of reusable devices' on the device, with certain exemptions, are applicable both in the USA and in the EU. Both bar code and Human Readable Format (HRI) are required by the EU.

EUDAMED

"European Databank for Medical Devices (EUDAMED)" is the database used for the collection of information regarding the medical devices and the IVDs. The earlier version of the EUDAMED had the provision only to the European authorities. The data could not be viewed by the person authorized of the device also. There wasn't any provision to correct the data. Due to these, many mistakes in data took place; a change to this database was made with the new regulation and EUDAMED was also updated (Bayrak and Çopur, 2017).

A "summary of safety and clinical performance" for Class C and D IVDs will be part of EUDAMED. The NB will evaluate and uploads this document to EUDAMED. The database will also include surveillance and post-market surveillance data (Institut,

2019).

The updated version of EUDAMED will have the data of the device entered by the owner itself and the data can be corrected and viewed anytime. The little amount of the data will be available for the public. The quality of the data will be the responsibility of the owner itself (García-Rojo *et al.*, 2019).

The EDUMED will also be extended to the member states of the EU for the uploading the summaries of market surveillance, reports of inspection, reporting of the unacceptable risk associated and information on the measures to be taken for the protection.

The introduction of new concepts of the following are made,

1. Economic Operators entering data will be identified by their Single Registration Number (SRN).
2. A device will be identified by its UDI. For the device module, an international nomenclature will be made available for free.
3. Clinical Investigations or Performance Studies will each have their Single Identification Number (SIN).
4. Incident reports will automatically be assigned a reference number (the responsible Competent Authority will add its own additional case number). Incidents can be described using international nomenclature for incident and root cause identification.
5. A Field Safety Corrective Action (FSCA) will automatically be assigned a reference number (the responsible Competent Authority will add its own case number).

Clinical evidence and post-market performance follow-ups are introduced as new concepts for IVDs. Clinical evidence indicates theoretical performance, empirical credibility, and medical performance, and their relationship to each other. Clinical evidence is based on clinical data and performance evaluation of an IVD to ensure it meets the purported clinical benefits and safety. The medical advantage is a device's positive impact on its purpose or on patient or public health management. The clinical evidence supports the intended purpose and is focused on an ongoing quality assessment process (Boumans, 2017). This need to be planned with a performance evaluation plan; these requirements will ensure identification of outdated and underperforming devices for non-compliance, which may stimulate innovation. The Performance Evaluation Plan will describe how to demonstrate,

1. Scientific validity (Scientific Validity Report) (Factsheet for Manufacturers of in vitro Diagnostic Medical Devices, 2017)
2. Analytic performance (Analytical Performance Report)
3. Clinical performance (Clinical Performance Report)
4. Performance evaluation (Performance Evaluation Report).

CONCLUSIONS

This study will provide a clear view of what new changes have been made to the IVDR in the EU, showcasing the newer improvements made like the UDI changes accompanied i.e. the attaching of device unique number and EDUMED database, development for the Device information and storing. This can lead to a completely new IVD technology system in the European Union.

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