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WHITEPAPER

SOFTWARE, ARTIFICIAL INTELLIGENCE AND MEDICAL DEVICES - WHAT'S UP?

Javier Varela
Regulatory Affairs Manager
javier.varela@pharmalex.com

With over six years experience in Regulatory Affairs and Quality Assurance, Javier Varela joined PharmaLex Spain, S.L. in 2018 as Team leader of Medical Devices. His role involves assisting other companies in the registration of new medical devices and providing advice in the transition to MDR 2017/745. Prior to this, he worked at Tedec-Meiji Farma, S.A, as a Regulatory Affairs and Quality Assurance technician of medical devices. Here he focused on the registration and maintenance of the company's medical devices portfolio according to the MDD 93/42/CEE requirements and providing support for international registrations of these products in FDA, ANVISA and MENA countries.

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Introduction

In recent years developers have invaded the markets with a multitude of health and lifestyle apps, turning our smartphone into a potential portable clinic. Our mobile devices are able to measure our heart rate, our physical activity and even they can be connected with other products to save our vital signs in the cloud and generate statistics that can be shared with our doctor in real time.

The implementation of artificial intelligence (AI) for the interpretation of data and decision making is becoming commonplace in our lives. AI is also helping with issues related to our health; enabling us to better dose medications or help doctors in the diagnosis of diseases.

Healthcare decisions are increasingly relying on information provided by the output of software and can impact clinical outcomes and patient care.

Whilst software is not something physical – it is lines of code that translate into electrical impulses in electronic devices – it can also be classified as a medical device.

Definition of a Medical Device

Medical devices in Europe are currently regulated by Directive 93/42 / EEC but as of May 26, 2020 shall enter into force Regulation 2017/745 also known as MDR. For the purpose of this article we will only consider the new regulation.

The MDR establishes in its definition that a medical device is:

'Medical device' means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations,*

and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means. [1.1.]

The following products shall also be deemed to be medical devices:

- *devices for the control or support of conception;*
- *products specifically intended for the cleaning, disinfection or sterilisation of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.* [1.1.]

How can I know if my software is a medical device?

If you have developed an application (app) for health or you are thinking of developing one, you should ask yourself the following questions before putting it on the market.

1. What is the purpose of my software?

It should be borne in mind that not all apps intended for health are a medical device. For example, apps with the purpose of maintaining healthy habits or improving sports performance are not medical devices. Nor those that remind patients to take medication.

Neither are apps considered medical devices if they store or transfer clinical data for statistical control and use by the patient or the doctor, so long as they do not interpret the data. However, the inclusion of an alarm if the values are outside an established range or the use of algorithms to reach a diagnostic conclusion or aid in the diagnosis or dosage of medication, would make this product a medical device.

2. Is it combined with other products? What function do you perform with these products? Does the purpose of these products change?

If software is combined with other health products, we must consider what function is performed. If it only transfers data collected by these devices or stores and organizes the information, it would not be a medical device.

Also, if your software is an integral part of the device, it will be part of the medical device itself. For example, software that controls the flow rate or pressure power of a hydraulic mechanism of a medical device, does not require to be certified separately.

If you perform an interpretation of the data of these devices for the purpose of diagnosis or you incorporate new functions as alarms for monitoring your software will be a medical device.

In addition, if you modify the intended purpose of a product by including it in the definition of a medical device or by modifying the intended purpose of the manufacturer of a medical device, it will be a medical device.

In summary, in case the intended use of your software is in line with the definition of a medical device or it modifies the intended use of an existing device and it is not an integral part of this device, your software is most likely a medical device. [1.6., 1.7.]

You can find further information in the following guides:

- Guidance: Medical device stand-alone software including apps (including IVDMDs), Medicines & Healthcare products Regulatory Agency (MHRA)
- MEDDEV 2.1/6 July 2016, GUIDELINES ON THE QUALIFICATION AND CLASSIFICATION OF STANDALONE SOFTWARE USED IN HEALTHCARE WITHIN THE REGULATORY FRAMEWORK OF MEDICAL DEVICES

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Classification

It seems that my software meets any of these criteria, now what?

If your software can be considered a medical device, the next step will be to determine the classification of your product.

Manufacturers of medical devices will need to define the classification of their products to determine the route to certificate their products; this is done using the classification rules in Annex VIII of MDR.

Medical devices can be classified in four groups depending on their risk.

The classification of the software can be performed by the following rules and 'implementing rules'. MDR includes a new rule specific for software.

IMPLEMENTING RULES

- *Software, which drives a device or influences the use of a device, shall fall within the same class as the device. If the software is independent of any other device, it shall be classified in its own right.* [1.1.]

Rule 11

Software intended to provide information which is used to take decisions with diagnosis or therapeutic purposes is classified as class IIa, except if such decisions have an impact that may cause:

death or an irreversible deterioration of a person's state of health, in which case it is in class III; or

a serious deterioration of a person's state of health or a surgical intervention, in which case it is classified as class IIb.

Software intended to monitor physiological processes is classified as class IIa, except if it is intended for monitoring of vital physiological parameters, where the nature of variations of those parameters is such that it could result in immediate danger to the patient, in which case it is classified as class IIb.

All other software is classified as class I. [1.1.]

As showed in the table above, software can be classified in all classes from Class I to Class III.

For each class there is a list of requirements which must be complied with. In addition, some of the classes give you different routes for certification – self certification or the appointment of a Notified Body. The majority will use the latter to obtain the certificate.

Certification Route

Once we know the classification, we must choose a certification route.

CLASS I – LOWER RISK

- Self-certification

If your product is a Class I and has not a measurement function or has not to be combined with other health products of higher classification, the manufacturer can include the CE mark directly on his product if he has previously carried out the following actions:

- Develop a technical dossier of the product (Annex II MDR).
- Make sure that the product complies with the essential requirements of the regulation Annex I and Annex III MDR.
- Ensure the product has a quality management system to maintain compliance with the essential requirements throughout the entire lifecycle of the product.
- Issue a declaration of conformity (Annex IV)
- In addition, in some countries the manufacturer must have a manufacturing licence for medical devices and in others, they must simply communicate their activity to the competent authority and notify the list of products that are manufactured.

Class IIA – MEDIUM RISK

- Chapters I and III Annex IX Quality Management System (QMS)

or

- Section 10 or 18 of Annex XI Production QMS

CLASS IIB – MEDIUM RISK

- Chapters I and III of Annex IX QMS

or

- Annex X together with Annex XI Type examination and production QMS

CLASS III – HIGHER RISK

- Annex IX QMS

or

- Annex X and conformity assessment Annex XI Type examination and production QMS

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If the classification of the product is a Class IIa, IIb or III, the manufacturer will have to prepare the same documents than for a Class I but it will be necessary to look for a Notified Body that will evaluate these documents and the product and will be granted a CE Certificate.

The Notified Body will perform an evaluation of the technical dossier and will perform audits to the manufacturing locations to verify that the manufacturer's quality management system and manufacturing process meet the essential requirements.

As seen above depending on the type of classification, a product can follow different routes of certification, nevertheless given the changing nature of the software and its potential to be modified and updated, it is preferable to choose the route defined in Annex IX QMS.

Regulatory Compliance

How can I meet all the requirements to register my software as a medical device?

Quality Management System (QMS)

QMS principles for many industrial sectors can be found in ISO 9000 standards, although in the medical device sector, the reference standard is ISO 13485 – Medical Devices-Quality Management Systems-Requirements for Regulatory Purposes.

What is a quality management system?

In a very simple way, it can be defined with the following sentence:

"Say what we do, do what we say and be able to prove it."

Say what we do: develop a quality manual, quality policies and procedures that explain our manufacturing process, design, development, validation, selection of suppliers.

Do what we say: comply with these procedures.

Be able to prove it: keep up-to-date digital or paper records that can show that we correctly perform the previously defined activities.

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On the other hand, software developers may be familiar with some other standards such as:

- Lifecycle management software - IEC 62304
- Usability - IEC 62366
- Safety - IEC 60601

You may even be using task and incident management tools or Scrum methodologies, which make it much easier to transition and convert your current documentation and management system to comply with the requirements of Regulation 2017/745.

We should consider that no standard ISO is mandatory in the EU but it is highly recommended to follow this as it provides presumption of compliance with the requirements. Furthermore ISO 13485 certificates may be required in other markets, therefore it should be considered from the start.

Briefly a QMS should define the following aspects of your company [1.3.]:

- Organization
- Resources and infrastructure management
- Document and record control
- Outsource activities management
- Analysis and improvement processes
- Lifecycle software management
  - Product design and development
  - Verification and validation
  - Release
  - Traceability
  - Maintenance
  - Withdrawal or corrective actions
- Risk management
- Vigilance activities

Verification and Validation

Verification and validation activities ensure that all elements from the software design and development, including any changes made during maintenance / upgrades, have been implemented correctly and that objective evidence of this implementation is recorded.

In simple terms, verification means confirmation that your outputs meet your inputs – that is to say your outputs meet your specifications. Have we manufactured the product correctly?

In the same way validation could be explained as the confirmation that your specifications cover the user needs. Have we manufactured the correct product?

Verification and validation should include scenarios that cover the expected clinical use and environment, considering the user demographic and risk profile. These activities should confirm that software safety elements work properly. [1.2.]

Manufacturers should employ rigorous impact analysis of changes made to software to ensure updates do not compromise the safety, effectiveness and performance of software.

These activities can be accomplished through structured human factors, testing using patients or clinicians and through automatic validations.

A consideration on AI software must be pointed out since this kind of software is dynamic – it is always updating itself to learn and provide a more accurate response to the data received. What is true for a static program with one input providing one output can be different with AI software, as the output can change while the learning process is still on-going. This makes both technical and clinical validation of AI software much more complicated. It forces manufacturers to develop more accurate validation processes, such as continuous validations, automatic validation processes, or releasing static versions of this AI software, keeping the dynamic version in a development environment and feeding it with real world performance data. [1.5]

Clinical Evaluation

The objective of the clinical evaluation is to compile clinical data to verify a device is safe and confirm its performance and effectiveness for its intended purpose.

For software, we can identify three main points:

- Valid clinical association of software
- Analytical / technical validation of software
- Clinical validation

Valid clinical association – confirm that the output provided by your software matches its targeted clinical conditions.

You can use literature searches, original clinical research, professional society guidelines, secondary data analysis, and / or clinical trials (new data generated).

Analytical / technical validation – confirm that the software correctly processes input data to generate accurate, reliable and precise output data.

Confirm that the software was correctly developed and demonstrate that the software meets its specifications and the specifications conform to user needs.

You will have evaluated this step in the previous phase.

Clinical validation – confirm that the output data achieves the intended purpose when used as designed by the manufacturer.

This clinical validity should be evaluated by the manufacturer during the software development phase and also post-market after distribution.

The manufacturer can demonstrate this by:

- existing data from studies for the same intended use
- existing data from studies for different intended use, justifying this extrapolation
- generating new clinical data for the specific intended purpose.

The post-market study can be managed by collecting user's feedback, complaints, adverse events, etc. This can provide new clinical evidence to include new functionalities to the software or restrict the current functions of the product.

Another possibility is that the manufacturer can decide to generate new clinical data for a specific intended use in order to include new functionalities or reinforce the current clinical evidence for the intended use of the software. [1.4.]

Risk Management

The Risk Management process should be integrated across the entire lifecycle of the software.

The risks should be identified based on the intended purpose, normal use and reasonably foreseeable misuse. [1.3.]

Although it is not the only way, one of the best methods to meet this requirement would be implementing a risk management system based on the ISO 14971 standard.

Labeling

Although the product is software, it must also comply with the labeling requirements. Please note that you must include the CE mark on your device.

If my device is an app that can be downloaded on smartphones, is not sold as a physical device where I can include a label in order to meet this requirement?

There are different alternatives, the CE marking, and data required for the labeling could be included in the screens and interface of the app or in the general conditions for use, provided that they are continuously accessible to users. In addition, if the app does not have an intuitive use, it should be accompanied by the instructions for use.

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Conclusion

Ahead of the new Regulation 2017/745 (MDR) being implemented in 26th May 2020, there are many things manufacturers of medical devices need to prepare for. This paper highlights just a few key points but there are many more that will need due consideration, including but not limited to;

- Unique Device Identifier in EU (UDI)
- EUDAMED – European Database of Medical Devices
- Person Responsible for Regulatory Compliance
- Vigilance of Medical devices:
  - Reporting of serious incidents and field safety corrective actions
  - Trend reports
  - Periodic Safety Update Report (PSUR)
  - Electronic system on vigilance and on post-market surveillance
- Post-Market Clinical Follow-up (PMCF)
- Requirement of prior local license or notification for manufacturing and import activities and obtaining Single Registration Number (SRN)
- Marketing notification obligations in certain countries

What is important is that if the MDR could apply to your product, we recommend you act now. With a wide range of apps on the market claiming to provide a health benefit, ensuring they all comply with the new regulation will take time and specialist expertise.

PharmaLex has extensive experience in medical device regulations both in the EU and the US. If you would like to discuss any of the points raised in this paper, or would like a more in depth review of your device compliance in accordance with the impending new regulation, please contact us on: contact@pharmalex.com.

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