Whitepaper

What is new under the EU MDR for software manufacturers?

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E-Health solutions, like web-based applications or those available in app-stores, have in recent years become more focused on contributing to health improvements. With more possibilities for these smart applications on phones and tablets to communicate between physician and patient there is clearly a potential for added value.

Physicians, when using these tools, can remotely monitor patient wellbeing, diagnose or even make treatment decisions based on clinical data. Also, the combination of functionalities like the ability to obtain personal health data via measurement, retrieval from archive and calculation through algorithms gives software devices significant clinical importance.

This all sounds great and is great because these tools potentially increase healthcare efficiency by reducing cost and effort for patients, physicians and health institutions. Also, patient involvement in managing their health is seen as a step forward. One essential requirement, however, is that these products should also be effective and safe and be applied for what they are made for. One way of securing this is compliance to the current EU legislation for medical device software and compliance to international standards.

The current risk management standard of 2012 (ISO 14971 [1]) valued software failures as something very difficult to assess in respect to the rate of occurrence. The EU harmonized standard on software development (ISO 62304 [2]) takes on a conservative approach, i.e. when considering a hazard that might be software related one should assume a 100% probability of occurrence of that hazard in the risk evaluation. Not surprisingly there are some examples like failing ventilators, critical care machinery software just shutting down or medication dosing apps that had incorrect algorithms. These incidents related to software but also earlier issues, like the PIP breast implant scandal have triggered the call for more control over medical devices in general. In relation to software some initiatives were started by agencies to check more strictly software product compliance to regulations and to international standards. In 2014, the Dutch

inspectorate (IGZ) found some manufacturers to lack the right procedures and even fined three app-manufactures, two for not notifying their software as a class I CE device with diagnostic functionality and one for applying CE marking without fulfilment of the relevant legal requirements [3]. The main weak points were in risk management, clinical evaluation and in procedures for product surveillance.

At current, the field is in a transitional period with still having the Medical Device Directive (MDD) [4] in place whilst also having, since 2017, the new EU Medical Device Regulation (MDR) [5]. For most products, the risk class will remain the same under the new MDR, but not for software. Due to a last-minute update to the software risk classification rule (MDR Annex VIII rule 11), by one of the EU member states. That update pushes most of the software products into a higher, more regulated risk class as of May 2020. Where in the past self-certification as a class I, lowest level, was the default for software now the same software under the MDR will most likely be a class IIa or higher requiring pre-approval by a Notified Body. And this means, a larger evidence base in regards to procedures, documentation and market surveillance.

To elaborate more on what the new Regulation will bring for software, this paper explains this in a topic-oriented overview. Before we go there, however it is important to give clarity on how you can determine if your software tool is a medical device in the first place.

Medical device Qualification and Classification – a focus on software

To determine if software is a medical device the official EU definition is leading. The definition can be found in both the EU Medical Device Directive (MDD) as and in the new MDR, in the relevant parts for software they are the same and state:

> *'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, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means…"* - [4] *and* [5]

In the definition most important is to compare it with the intended use of the product as you, as a manufacturer, have formulated that for your product. The intended use is not something the end user is able to decide on. It has to be determined by the manufacturer and as such formulated in the instructions for use or in the way it is functionally provided to the end user.

To assist in the qualification and classification, EU guidance documents have been provided by the European Commission. These are the co called EU MEDDEVs. Currently they refer to the MDD only, however there are efforts

ongoing to transform them as guidance to the MDR as well. MEDDEV Guidance 2.1/6 [6] is specifically made for software used in healthcare. MEDDEV Guidance is non-binding guidance but based on recent decisions of the EU highest court of justice MEDDEV guidance is confirmed to be the intended proper interpretation of the legislation (e.g. 7 December 2017, the CJEU issued its judgment in Case C-329/16).

The guidance makes clear that the decisive factor in the medical device qualification is whether the characteristics and functionality of the software is specifically intended by the manufacturer to be used for one or more medical objectives, including the diagnosis, prevention, monitoring, treatment or alleviation of disease. It does not matter whether the software acts directly or indirectly on the human body. As a comparison, a knife when used in an operating room during surgery might be the same knife as being sold in a kitchen appliances store, but due to the difference in intended use, different requirements on the knife need to be executed and documented. This indicates that more than the product itself, the intended use determines which requirements need to be fulfilled.

For your orientation, some more examples are given below. They come from the Borderline Manual (version 1.19) [7]:

Qualified as medical devices:

- App for comparing pictures of moles/birthmarks and providing a probability estimation for melanoma. The app has image processing algorithms and does comparisons. Since there is an action on data other than storage with a diagnostic intend for individual patients, this qualifies as a medical device.
- Cognitive remediation and rehabilitation program software that supports and manages the progress of patients via targeted stimulation of cognitive function by using interactive games and exercises. Since the intent is to support treatment of disease, injury of handicap, this is a medical device.
- Mobile apps for processing ECGs

Not qualifying as medical device:

- A mobile app intended to improve the quality of communication between patient and caregiver, including storage of notes and pictures for later use (e.g. of moles), without any data transformation via algorithms or picture enhancements or any intend to diagnose or monitor changes actively.
- Application for viewing anatomy of the human body for educational purpose, including more than only simple data search, but without the direct use for the benefit of an individual patient.
- Tumor classification (e.g. TNM) software based on text book variables. Variables are the inputs and the application performs a simple search in the text book information. The software facilitates the search and use of an international guideline which physicians usually consult via electronic file, or in paper format.

If the software is not a medical device, it is wise to document the justification. Also, is it important to document your intended use of the product and any health risk analysis related to it. To further assure the product also stays a non-medical device, it is recommended to monitor the actual use of the product in the market, to check how your sales force promotes the software and to evaluate miss-use that could bring it under the medical device definition. One way to do so is to check product complaints over time and to put out user experience questionnaires periodically.

If your software qualifies as a medical device, the correct risk classification is to be established. For the classification, both the MDD and the MDR provide criteria in their ANNEXES covering device classification. New is that the MDR has a new rule specifically dedicated to software and as indicated most software products will end up in a higher risk class as before.

EU Medical Device Directive (MDD) and Regulation (MDR) – The transition period

The new Medical Device Regulation (MDR) has become effective as of 25th May 2017 and will become applicable and replace the Directive as of 26th May 2020. This means that all current class I software products as of May 2020 need to be reassessed and most likely need to be (re)certified (as class IIa) by a Notified Body in order to ensure continued market access. At current, no Notified Body has been granted this ability yet, but it is expected soon in the first quarter of 2019 with the hope that the first devices will be granted market access under the new MDR in the second half of 2019.

In relation to MDD, MDR and the transition period [8][9], each manufacture with new software products has now three options:

1) Self-certify your class I software under the current MDD, but knowing that it can only be marketed till May 2020. This means no delay, but limited access in time.
2) Self-certify your class I software under the MDD, and in parallel seek a Notified Body that will assess the full upgraded dossier in 2019/2020 to ensure continued market access. This means continuous work on the upgrading of the technical documentation and procedures, with no delay to market and with a good chance for continued access.
3) Seek a Notified Body that will assess the dossier under the MDR as soon as possible and gain market access in due time. Be aware however that Notified Bodies are currently not designated yet to assess your product under the MDR. This means that your market access date remains a question mark until that time.

For already marketed medical devices there are also 3 options:

1) Do nothing. If your class I software product is currently marketed but you have no interest in marketing it beyond May 2020, you do not need to take action. For higher classes, like class IIa software products, you have a valid product certificate and until this validity expires, the product can be placed on the market until May 2024 the latest.

2) Extend the validity or your product certification by asking for an early re-certification prior to May 2020. With such activity an early expiration after May 2020 may be avoided, but also this is only delaying the inevitable. This option does not apply for class I devices, since they do not have a certificate, unless you change the product (e.g. intended use/user or functionality) to meet criteria of a higher risk class. This could mean a considerable effort.

3) Seek for an assessment under MDR by a Notified Body as soon as possible, since already before May 2020 products are allowed to receive MDR compliance certificates. As of Q3-4 2019 the first Notified Bodies are estimated to be able to give you a CE marking under the new regulation.

The new MDR requirements

The MDD had a focus on pre-approval requirements, but the MDR asks for more. The new MDR expects control over procedures and documents over the full life-cycle of a product. This shift results in more requirements for topics like:

1) Clinical evidence
2) Post market surveillance
3) Tracking of product
4) Risk management
5) Technical documentation (registration dossier)
6) Quality management system

What will not change for software is the best practices of being compliant to standards like IEC 82304-1:2016 on Health software -- Part 1: General requirements for product safety [10] and IEC 62304:2006, Medical device software — Software life cycle processes -as amended (2015) [2]. To elaborate on what is now expected for the identified topics, some explanation may benefit your efforts:

1) Clinical evidence :New is that all Medical devices require a Clinical Evaluation Plan (Annex XIV), an evaluation and a Report. The plan should assure a systematic and planned process to continuously 1) generate, 2) collect, and 3) assess clinical data on your device in order to verify the safety and performance including the benefits.

2) Post market surveillance: New is the requirement for a Post Market Surveillance Plan including Post Market Clinical Follow, if applicable. This should describe the proactive collection of clinical data with the aim to confirm safety and performance over the expected lifetime of the device with factual evidence. A Periodic Safety Update Report (PSUR) should be made every one or two years reporting on a conclusion on benefit risk, based on product surveillance data like incident reports, safety concerns, etc. The report should also include a presentation on preventive and corrective actions taken, volumes of sales and frequency of use.

3) Tracking of product: The main tools for tracking the product over the life time is the use of data in the EUDAMED database and data on the product itself by means of a Unique Device Identifier (UDI). Agencies and Notified Bodies will put data on your product in the EUDAMED database, but you as a manufacture need to do that also. To gain access a Single Registration Number is handed out to you by your competent authority. The EUDAMED database will issue the UDI and the UDI will be based on a for-free international nomenclature. EUDAMED will also be the means to track incident reports and field safety corrective actions. According to the MDR, EUDAMED should go live on 25 March 2020 at the latest (article 34.1 MDR, article 30.1 IVDR [11]).

4) Risk Management: The MDR, as did the MDD, confirms that compliance to standards will give presumption of compliance to relevant aspect of the regulation. The application of the ISO standard 14971 [1] on Risk management and that for software development IEC 62304 [2] is advised to be adhered to. In regard to risk management, more work from manufacturers is anticipated because under MDR there will be more points in time where new data from the market use may reveal new risks.

5) Technical documentation :The MDR much more than the MDD gives direction on technical document requirements, prescribing more than 40 specific elements for the content of the primary technical documentation, and more than 15 additional elements on post market surveillance (see Annexes II and III of the MDR). Not all may apply to software, but those applicable need to be kept up to date and made available to agencies upon request, with the note that in legal disputes, agencies might share these documents with plaintiffs. The technical documentation represents the entirety of the documents describing a device. It therefore includes the device's design, development, Verification and Validation (V&V) (including clinical and performance validation) as well as its regulatory status. The technical documentation should be structured and presented, in such a way, as to facilitate its review and assessment by the Notified Body. The MDR now provides, in Annexes II and III, detailed instructions on what is the minimum content of technical documentation. Within this technical documentation, manufacturers must provide objective evidence to show that their device satisfies the requirements detailed in Annex I of the MDR. Where requirements are not applicable an explanation as to why they do not apply, must be provided.

6) Quality Management System for SW companies: A quality management system (QMS) is a set of processes and documented procedures focused on consistently meeting customer and other relevant requirements. To have a QMS is a MDR requirement and in case it is certified, one can benefit from its presumed compliance to the

regulation. This is not new under the MDR but is again confirmed. Having an ISO 13485 [12] certificate on your QMS will remain a preferred situation for many manufacturers and their clients. The MDR instructs that your QMS should address amongst others the control of suppliers, risk management, clinical evaluation, product realization (including planning, design, development, production and servicing), post-market surveillance, incident reporting and management of corrective and preventive actions (including verification of them).

Requirements for the Manufacturer

Whereas previous requirements related to internal processes and documentation relevant to product realization and life-cycle management, the new MDR also addresses many requirements for agencies, Notified Bodies and manufacturers to facilitate the system. Here are some that are new for manufacturers in general:

1) A formal registration as a medical device manufacturer. The manufacturer will receive a Single Registration Number (SRN). The SRN will be issued by the Member State where the manufacturer is based.
2) Availability of a person responsible for regulatory compliance. Available could be within the organization or permanently and continuously at their disposal.
3) Provision of product data into the EUDAMED database, as soon as EUDAMED becomes in place.
4) Measures to ensure sufficient financial coverage in respect of potential product liability.
5) Be ready for and provide access to Notified Bodies that shall randomly perform at least once every five years unannounced audits on the site of the manufacturer.

Closing remarks

Software manufactures are one of the most impacted groups in regards to meeting compliance for the new MDR. Not only will the new requirements be relevant to them, but with the upgrade to a higher risk class the expectation on resources, procedures and documented evidence has significantly increased. Time is short and with the dependency for Notified Bodies to assess their products before May 2020, the next two years will for sure be much more uncertain than before.

References

[1] ISO, "ISO 14971:2019 Medical devices — Application of risk management to medical devices."

[2] IEC, "IEC 62304:2006+AMD1:2015 Medical device software - Software life cycle processes."

[3] IGJ, "Medische software doorgelicht," vol. 21 JUL, 2016.

[4] The Council of the European Communities, "COUNCIL DIRECTIVE 93/42/EEC of 14 June 1993 concerning medical devices." .

[5] European Parliament and the Council of the European Union, "REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices." .

[6] European Commission, "Guidelines on the qualification and classification of stand-alone software used in healthcare within the Regulatory Framework of Medical Devices," vol. 2.1/6, 2016.

[7] European Commission, "Manual on borderline and classification in the community regulatory framework for medical devices," vol. version 1., 2018.

[8] European Commission, "Factsheet for Manufacturers of Medical Devices," 2018, doi: 10.2873/66341.

[9] European Commission, "Factsheet for Authorities in non-EU/EEA States on Medical Devices and in vitro Diagnostic Medical Devices," 2018, doi: 10.2873/850249.

[10] IEC, "IEC 82304-1:2016 Health software — Part 1: General requirements for product safety."

[11] European Parliament and the Council of the European Union, "DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices."

[12] ISO, "ISO 13485:2016 Medical devices — Quality management systems — Requirements for regulatory purposes."

About Starodub

Reliable, Efficient and Knowledgeable

Starodub BV was founded in May 2014. The company started with one employee, the founder Valentyna Starodub. By today, our team has grown to round 20 employees and has a valuable network of specialized experts. We partner with (bio)pharmaceutical and medical device companies worldwide to ensure that regulatory requirements are met and business goals, such as quick market access and compliance, are achieved. Please check the Our services page to learn how we can support you with meeting your business goals.

Our lean and powerful team strives to be of added value to our clients. All employees are highly educated and obtained degrees in pharmacy, chemistry, biology or related. Our short reporting lines are key to finding the most efficient road to your success. One of our experts will be your primary contact and the team's collective knowledge and resources are available to give reliable advice and execute projects in the most efficient way. Together, we connect the dots and look beyond the scope of projects to make sure all aspects of importance are addressed.

At Starodub BV consistency and assurance of quality are considered as being highly important. A quality management system has been implemented and we strive to comply with GxP and ISO 9001/13485 constantly. In addition, we have an external board of control, acting as the sparring partner to set the optimal course for our company.

We strive to be a true partner to Our clients, who rate our services as ≥4.5 on a scale of 1 (poor) to 5 (excellent). This motivates us to maintain the highest professional standards and to implement continuous improvement.

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