What regulators expect from medical device manufacturers of software with artificial intelligence (AI) & machine learning (ML)

Q&A taken from our live webinar

1. What is the difference between software standardization between CE marking and FDA?

CE marking and conformity assessment in the EU is according to the requirements of Medical Devices Directive(s) /and EU MDR 2017/745.

The European Commission provides a range of guidance documents (MDCG endorsed documents) to assist with implementation of the regulations.

The US conformity assessment is based on 510(k) premarket submission or PMA/PMA supplement submissions made to FDA to demonstrate that the device to be marketed is safe and effective. The 510(k) route requires proving substantial equivalence (SE) to a legally marketed device (predicate device) that is not subject to Premarket Approval (PMA). The FDA provides publications on guidance for industry and FDA staff with respect to expectations for software submissions.

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The International Medical Device Regulators Forum (IMDRF) is a voluntary group of medical device regulators from around the world which develops internationally agreed upon documents for topics affecting medical devices and has a working group to develop guidance relevant for software.

2. What is the regulatory strategy for global Software as a Medical Device (SaMD) prospective at development level?

The manufacturer should determine their regulatory strategy according to the countries that the device is intended to be marketed and the regulations and guidance required to be complied with (See above for 1). A mapping or gap assessment may help to assist determination of the most appropriate strategy or course to follow.

3. What are the regulatory requirements for Software Requirement Specification (SRS) for Mobile Medical Application (MMA)?

Regulatory requirements are present in EU MDR 2017/745; including Annex I, and General Safety and Performance Requirement 17.3 which refers to mobile computing platforms.

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Applicable standards such as EN/IEC 62304 and EN/IEC 82304-1 also include requirements for software development including software requirements. Further guidance for example MDCG 2019-16 guidance on cybersecurity of medical devices may also provide input to a software requirements specification

4. Why do you identify EN/IEC 62304 as relevant, I thought for SaMD EN/IEC 82304-1 is relevant?

The scope of the EN/IEC 62304 is for the lifecycle requirements for Medical Device Software, processes and activities and tasks. The scope of EN/IEC 82304-1 is for application of safety and security of health software products and does not apply to health software intended to become part of specific hardware, medical electrical systems covered by IEC 60601/80601, In vitro diagnostic equipment covered by IEC 61010 series or implantable devices covered by ISO 14708 series.

SaMD is not defined in relation to 2017/745 and is replaced by software driving or influencing the use of a device and Medical Device Software (MDSW) which also defined in EN/IEC 62304 Amendment 1. Note that EN/IEC 82304-1 requires the use of software lifecycle processes defined in EN/IEC 62304 clauses 4.2, 4.3, 5, 6, 7, 8 and 9.

5. You mentioned IEC 14764. Is compliance with EN/IEC 62304 and ISO 14971 for the EU not sufficient?

The state-of-the-art changes over time and standards are not always sufficient. EN/IEC 62304, EN/IEC 82304-1 and EN ISO 14971 are applicable to medical devices together with other standards, guidance etc. which would represent state of the art. ISO/IEC 14764:2006 is applicable for software engineering and provides a framework for maintenance of software which may support or lead to improved development process.

IEC 14764 can support and lead to a deeper understanding and improved process for SaMD development.

6. Shall we follow the edition 2019 of ISO 14971 for CE mark of SaMD?

There are no harmonised standards currently to the regulation 2017/745 MDR. The EN ISO 14971:2019 is the latest version of the standard and can be applied for medical device software conformity assessment as relevant for state of the art.

7. Which document should we refer to for Software changes in Europe?

The presentation references IMDRF/SaMD WG/N10FINAL:2013 5.3 SaMD Changes which includes information on software changes and may be found at imdrf.org/documents/documents.asp

Relevant standards for software lifecycle processes, for example EN/IEC 62304 and EN/IEC 82304-1 also cover software changes and maintenance process.

Change management is also relevant in relation to medical devices quality management system process and ISO 13485:2016 (e.g. Clauses 7.3.9, 7.3.10, 7.4.2, 7.4.3, 7.5.6, 7.6, 4.1.6), and for conformity to Medical Devices Directive(s) /Regulation (EU) 2017/745 on medical devices and conformity assessment to Annex IX, X, XI.

MDCG 2020-3 includes guidance on significant changes regarding transitional provision under article 120 of the MDR with regard to devices covered by certificates according to MDD or AIMDD.

NBOG BPG 2014-3 contains guidance regarding software changes that would be considered 'substantial' for devices covered by MDD or AIMDD certificates.

8. Should we refer to the US guidance for changes in software for CE Marking?

No, the US guidance is directed for the US although the artificial intelligence/ machine learning (AI/ML) discussion paper is the proposal of the US FDA and the EU could incorporate in future guidance documents or adjustments of the legislations.

9. Is IMDRF guidance applicable to US legislation only or also applicable to EU legislation?

The IMDRF guidance is not legally binding for the US or EU. Only the US or EU legislation is legally binding. However, the IMDRF guidance is a global agreement from the regulators, and the regional or national legislations reflect the IMDRF guidance.

10. Is there a difference in the approach for machine learning (ML) software that is regulated under MDR vs under IVDR?

No, the requirements of the regulations apply to both at the moment, although it is under review.

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11. When can we expect the AI/ML-based approach of FDA to be implemented? Any companies do you know of which got FDA clearance on this new approach?

There is no timeline given by the US FDA for the AI/ML-based approach. The status is a proposal and in discussion with other stakeholders, e.g. industry.

12. Should we refer to the US guidance for changes in artificial intelligence for CE Marking?

No, the AI/ML discussion paper from the US FDA is a proposal. For CE marking refer to the EU 2017/745 (MDR) and the MDCG and IMDRF guidance documents applicable.

There may be further regulations and guidance in the future.

13. How detailed should an AI/ML software be documented? Should the network architecture be documented, and the effect of different layers? Or only the purpose of the algorithm?

An AI/ML-software is a medical device itself as medical device software (MDSW) or as software that drives or influences a medical device. State of the art standards (EN/IEC 62304, EN/IEC 82304-1) provide a framework for software lifecycle development including device architecture and detailed design. Note that EN/IEC 62304 has increasing requirements around documenting architecture and detailed design based on software safety classification (i.e. Class 'A' has less stringent requirements while Class 'C' has more stringent requirements). The regulation 2017/745 also has requirements relating to general safety and performance requirements, IT environment including disclosure in instructions for use.

MDCG 2019-16 Guidance on cybersecurity for medical devices was made available in December 2019; https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_cybersecurity_en.pdf

14. Is there a guideline for the verification strategy of SaMD containing artificial intelligence/ machine learning (AI/ML)?

There is no guidance finalised at this time. The design procedures as required by EN ISO 13485 determine the design and development process and requirements for verification and validation including plans and documented output. The current regulations including (EU) 2017/745 and other guidance documents (MDCG, IMDRF, FDA) are developed relating state of the art. Further guidance may become available at a future date.

15. Is this new regulatory pathway (with pre-specification/ Algorithm Change Protocol) already in place, or what is its status?

The new regulatory approach is a proposed regulatory framework to enable the FDA and manufacturers to evaluate and monitor software products with AI technology. The regulators are in the process of determination of guidance and regulatory approach with such devices.

16. If I understand correctly, there is no way under MDR that a real-time updating/ changing algorithm can have a CE-mark at all. Is that correct?

The requirements of the regulation 2017/745 (MDR) applies in the EU and conformity assessment apply to all devices applied for where notified body assessment is needed according to general performance and safety requirements to the state of the art with risk management framework. An application for such a device could be applied for, however the outcome of conformity assessment would determine whether such a device could achieve CE mark. The topic of artificial intelligence (AI) technology is under discussion amongst regulators and notified bodies and may result in further guidance to such a device being able to achieve a CE mark.

In the USA the 510K premarket submission applies to substantially equivalent devices to a legally marketed device; the proposed discussion paper from the FDA is a framework relating to continuously updating devices and would allow manufacturers to plan modifications during pre-market review and an approach for modifications and does include scenarios which may not be appropriate (Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML) – based software as a Medical device)

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17. Under the current MDR rules, can a software collect data, e.g. vital parameter, to be used offline to develop the algorithm and then get clearance from a notified body (NB) before implementing changes?

The design and development process may include use of and/or collection of data to aid in the device development and relevant regulations would apply, for example the Data Protection Act GDPR and Clinical Trial Regulation (EU) 536/2014. These data may be used for the conformity assessment and evidence of performance and safety with a notified body.

18. Let's say a parameter is introduced in the SaMD, which does not alter the intended use but if that feature is clinically relevant, is new clearance or submission required? Example: radiological image post-processing software including a new feature for lesion measurement.

Yes, a new parameter, which is outside the intended use needs an additional conformity assessment according to EU MDR 2017/745 Annex IX, X, XI. Each change of intended use is a significant change.

19. How do you concretely define the borders what in the algorithm is allowed to change? How do you justify the borders chosen for your algorithm?

The manufacturer defines the architecture of the device design including software units and algorithm functionality within each part of the device. Such architecture and design may assist with definition of borders/boundaries in conjunction with requirements of applicable standards and regulations, for example EN/IEC 62304, EN/IEC 82304-1 and EN ISO 14971 (application of risk management to medical devices), 2017/745 etc. for safety and performance taking into account the state of the art and clinical data. For software changes refer to questions 1 and 2 above.

20. Can you show an example for the algorithm change protocol? (ACP)?

For now, no SaMD product is in the market relating to ACP.

The design and development process may include use of collection of data to aid in the device development and relevant regulations would apply, for example the Data Protection Act GDPR and Clinical Trial Regulation (EU) 536/2014. These data may be used for the conformity assessment and evidence of performance and safety with a notified body.

An example is endoscopy software, which supports the surgeon to identify cancer cells in an early stage. This software could have live data collection and conform with relevant regulations with anonymous data process and code improvement in the software lab of the endoscopy manufacturer.

21. The software UDI guidance talks about the significant changes (which needs to change the DI) a little bit, could we use that as the definition of the significant changes of the software?

The manufacturer quality management processes in relation to EN ISO 13485 should have procedures relevant for determining significant changes. MDCG 2020-3 guidance may be used as an input to determination of a significant change together with any other relevant factors for example change to intended use or technology change.

22. Would you consider a change in Software of Unknown Provenance (SOUP) a possible ‚significant change' in the EU or the US? How about a change in the validation process of SOUPs?

Yes, a change in a SOUP or validation process of SOUP, may be a significant change. There are requirements in standards such as EN ISO 13485, EN/IEC 62304, EN/IEC 82304-1 and legislation of the MDR relating to design and development, software maintenance, changes and risk management.

23. Which points are important to consider validating a software based on AI or ML clinically?

The design procedures as required by EN ISO 13485 determine the design and development process and requirements for validation including plans and documented output.

The MDCG guidance document MDCG 2020-1 details guidance related to clinical evaluation (MDR) / performance evaluation (IVDR) of medical device software. Conformity assessment to the requirements of the regulation 2017/745 (MDR) is also required for CE marking.

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https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020_1_guidance_clinic_eva_md_software_en.pdf

24. Do you have any information on clinical evidence data to be provided on SaMD with AI/ML class I or III?

The design procedures as required by EN ISO 13485 determine the design and development process and requirements for validation including plans and documented output.

The MDCG guidance document MDCG 2020-1 details guidance related to clinical evaluation (MDR) / performance evaluation (IVDR) of medical device software. Conformity assessment to the requirements of the regulation 2017/745 (MDR) is also required for CE marking.

Classification to the requirements of the regulation 2017/745 Annex VIII including Rule 11 apply for software for all device risk classes. State of the art standards, for example EN/IEC 62366 may also be used.

25. How to deal with the software used in proof of concept stage in a medical device development? Should we validate all the software used in this stage when we test different aspects of the product?

The design procedures as required by EN ISO 13485 determine the design and development process and requirements for validation including plans and documented output.

The plan may include validation of software at proof of concept stage but should also be appropriate to the completed device with changes revalidated. At minimum, manufacturers should ensure that any software code that is retained from the proof of concept stage and makes it into the final product software should be subject to software development and testing requirements per EN/IEC 62304 and any other applicable standards.

26. What is the difference between computer system validation and software validation? How do you determine if you need validation or verification? Can you please elaborate?

A computer system validation is a validation testing (establishment of objective evidence) of a complete system (software installed on hardware in intended environment with an operating system and any recommended software patches that the device specifications conform to the user requirements or needs and that the device system works as intended. Computer system validation is often applied to non-product software that can affect final medical device quality. Examples include software used in the manufacturing process (see ISO13485 clause 7.5.6, 7.6) and software used in the quality management system (see ISO13485 clause 4.1.6), such as document control system software or requirements management software.

The design procedures as required by EN ISO 13485 7.3 determine the design and development process and requirements for verification and validation including plans and documented output. The plan for each device makes a determination of verification and validation applicable to that device to provide objective evidence that specifications and applicable requirements or user needs are met and that the device works as intended with appropriate performance and safety.

27. Can you please give an example of software validation and verification? E.g. what kind of testing is done in validation and verification? Is black box testing and white box testing part of validation and verification? Is the software developer responsible for any kind of testing related to software and to document them?

The design procedures as required by EN ISO 13485 determine the design and development process and requirements for verification and validation including plans and documented output. Medical device software validation is the validation testing (establishment of objective evidence) of the medical device software to demonstrate that the software (either alone or when used as part of a system) is capable of meeting user requirements or needs and works as intended. Note that EN/IEC 62304 does not cover medical device software validation and covers only up to SOFTWARE SYSTEM VERIFICATION.

Medical device software validation is the validation testing (establishment of objective evidence) of the medical device software (either alone or when used as part of a system) is capable of meeting user requirements or needs and works as intended. Note that EN/IEC 62304 does not cover medical device software validation and covers only up to SOFTWARE SYSTEM VERIFICATION.

Medical device software verification is the verification testing (establishment of objective evidence) that the product requirements (software requirements specification) are met confirming that the device output meets design input. White box and black box testing may be used within the plans for the device. White box testing usually requires intimate knowledge of the code and may best be conducted by a software developer. White box testing would typically be considered part of software verification (e.g. software unit testing and software integration testing per EN/IEC 62304). Black box testing could represent either verification or validation testing. Software developers may be responsible for some aspects of the verification testing; however, verification and validation testing should be independent of design.

28. How do you validate an off-the-shelf (OTS) software like Amazon Web Services (AWS) cloud services if it is an integral part of SaMD Product?

A computer system validation is a validation testing (establishment of objective evidence) of a complete system in intended environment with an operating system and any recommended software patches or off the shelf software (OTS) that the device specifications conform to the user requirements or needs and that the device system works as intended. The design procedures as required by EN ISO 13485 determine the design and development process and requirements for verification and validation including plans and documented output. The plan for the device should include any requirements for verification and validation of software or services. There is MDCG 2019-16 guidance also available relating to cybersecurity of medical devices.

https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_cybersecurity_en.pdf

Note that OTS software incorporated into a medical device would be considered as SOUP per the EN/IEC 62304 definition and would be subject to EN/IEC 62304 clauses required for SOUP.

29. Where can I get sample size requirements for software test cases?

A performance test model or clinical study needs to be sufficiently statistically powered to provide performance / clinical significance, and statistical output to the state of the art and requirements of appropriate regulations.

MDCG 2020-1 Guidance on clinical evaluation (MDR)/ Performance evaluation (IVDR) of medical device software was made available in March 2020, and the FDA also has published guidance relating to clinical trials, for example E9 Statistical Principles for Clinical Trials, Statistical considerations for clinical trials during the COVID-19 public Health Emergency Guidance for Industry. Note that at the level of software verification, a sample size of one execution may be considered acceptable if the software behaviour under test can be considered deterministic in nature. Where deterministic software/system behaviour cannot be assured, a statistically based sample size selection approach should be used. The manufacturer will need to provide sample size justifications based on risk and on whether the testing can be considered deterministic in nature.