Congenius

Congenius Whitepaper

Artificial Intelligence in medical devices

Current & future Regulatory landscape

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Introduction

Introduction

Artificial Intelligence (AI) has the potential to revolutionise the healthcare industry by enhancing diagnostic accuracy, treatment efficiency, and patient care.

AI technologies, such as machine learning (ML), natural language processing (NLP), or computer vision (CV), have shown promise in various medical applications, including image analysis (radiology), disease prediction, drug discovery, and personalised medicine. AI-enabled medical devices leverage machine learning algorithms and advanced data analysis techniques to provide actionable insights from medical data. These technologies can help physicians make more informed decisions, improve patient outcomes, and streamline healthcare processes.

This whitepaper provides an overview of the regulatory frameworks for incorporating Artificial Intelligence (AI) in medical devices in the European Union (EU) and the United States (US). It examines the current key regulatory considerations and approval pathways for AI-driven medical devices in the EU and US and outlines the current AI standardisation efforts, as well as a projected view of what the future may hold from a regulatory perspective for AI-enabled medical devices in both regions.

Regulatory landscape in the EU

Regulatory landscape in the EU

The EU's regulatory framework for medical devices underwent a significant transformation with the introduction of the Medical Devices Regulation EU 2017/745 (MDR) and the In Vitro Diagnostic Regulation EU 2017/746 (IVDR).

AI-enabled medical devices are classified based on intended purpose and are subject to rigorous risk class dependent conformity assessment procedures.

As with any software, medical AI systems must first be assessed as to whether they qualify as a medical device within the meaning of the MDR. The “qualification as a medical device” is solely based on the intended purpose of the respective AI system in relation to the medical device definition in Article 2(1) of the MDR. AI systems intended to be used, alone or in combination, for a purpose specified in the definition of a medical device qualify as medical devices; and are subsequently classified according to the Implementing and Classification Rules laid out in Annex VIII of the MDR; classification Rule 11 is particularly relevant for software. MDCG 2019-11 provides further guidance assisting manufacturers in the qualification and classification of medical device software.

Manufacturers of medical AI systems, like other medical devices manufacturers, are subject to the obligations defined in Article 10 of the MDR, so before placing their products on the market, manufacturers must demonstrate the conformity of their products accordingly.

Specific requirements for medical device software can be found in the MDR in Annex I (General Safety and Performance Requirements) that are equally relevant for medical AI systems. However, the MDR does not contain any AI-specific requirements regarding safety and performance.

Regulatory landscape in the EU

Following “the idea that the safety of AI-based medical devices can only be achieved through a process-oriented approach”, in 2022, the Association of Notified Bodies for Medical Devices in Germany (IG-NB) published the document "Questionnaire Artificial Intelligence (AI) in medical devices".

This guideline contains a checklist for manufacturers and Notified Bodies outlining requirements such as competencies, intended purpose, software requirements, data management, AI model development, product development and post-market surveillance. Additionally, the IG-NB provides the following important differentiation in Section A of its guideline on the certifiability (CE-marking) of AI systems under the current EU regulatory framework:

> **"Static AI (AI that has learned and operates in a learned state, non-continuous learning) is in principle certifiable.” However, for static AI systems with black box behaviour (AI that does not explain how it arrives at a certain result), regulatory requirements “set limits on certification” and “the possibility of certification requires a review by the Notified Body and is a case-by-case decision.”**

Furthermore, according to the IG-NB, **“dynamic AI (AI that continues to learn in the field) is not certifiable in principle, as the system must be verified and validated (among other things, the functionality must be validated against the intended use).“**

In particular, Annex I GSPR 17.1 of the MDR that requires software-based medical devices to be “designed to ensure repeatability, reliability and performance in line with their intended use” poses specific challenges and limitations for certain AI-based medical devices.

Regulatory landscape in the EU

In a recent press release, the German Society for Biomedical Engineering in the VDE (VDE DGBMT) stated that **“innovation is hampered by the fact that continuous learning AI systems are currently not allowed to be marketed as medical devices in the EU”** and made a proposal for an alternative regulatory framework, primarily aimed at authorities, Notified Bodies and the European legislator.

This so-called **"anticipatory CE conformity assessment"** approach is characterised by the planning and approval of subsequent intended changes before the device is placed on the market, while changes that cannot be foreseen and cannot necessarily be anticipated would remain subject to a new conformity assessment procedure. This proposal leverages elements of the FDA’s Predetermined Change Control Plan (PCCP) and is based on the approach of “pre-determined” changes as currently proposed by the European draft Artificial Intelligence Act (AIA).

Regulatory landscape in the EU

Future European Artificial Intelligence Act (AIA)

Following their 2019 “Ethics guidelines for trustworthy AI” and the 2020 “White Paper on Artificial Intelligence”, in April 2021 the EU Commission marked a key milestone by publishing the draft Artificial Intelligence Act (AIA), proposing a uniform horizontal legal framework for the development, marketing, and use of artificial intelligence.

Therein, AI medical devices are classified as so-called high-risk AI systems and are subject to special market access "Requirements for high-risk AI systems" outlined in Articles 8 to 15 of the draft AIA. While these include requirements already known from the MDR such as establishing a risk management system and drawing up technical documentation, there are new AI-specific requirements included e.g., training, validation, and testing data for AI models or human oversight during the period in which the AI system is in use.

Chapter 3 of the draft AIA sets forth further "Obligations of providers and users of high-risk AI systems and other parties," which apply to providers of high-risk AI systems in a similar way to the MDR, for example, the establishment of a quality management system in compliance with the AIA and obligations for other economic operators, and new requirements, such as the obligation to retain the logs automatically generated by the high-risk AI system.

Regulatory landscape in the EU

Future European Artificial Intelligence Act (AIA) (cont.)

Concerning modifications, draft AIA Article 43(4) proposes “for high-risk AI systems that continue to learn after being placed on the market or put into service, changes to the high-risk AI system and its performance that have been pre-determined by the provider at the moment of the initial conformity assessment and are part of the information contained in the technical documentation […] shall not constitute a substantial modification” whereby, according to the draft AIA (recital 66), a substantial modification is one that could affect compliance with the AIA or that changes the intended purpose of the system.

While the VDE DGBMT acknowledges the draft AIA to be “a completely new type of CE conformity assessment for continuous learning AI systems, which has so far not been explicitly provided for neither by the German Notified Bodies nor in the MDR” it also considers it compatible with, and not conflicting with, the current legal framework of the MDR.

At present, the legislative process is currently ongoing and recently entered its final phase, the Trilogue - finalisation is not expected before the end of 2023. Once adopted, the regulation will come into force 20 days after its publication in the EUR-Lex Official Journal. It will apply 24 months after its publication date, but some provisions of the future AIA regulation may apply sooner.

Regulatory landscape in the US

Regulatory landscape in the US

Traditionally, the FDA reviews medical devices through an appropriate premarket pathway, such as premarket clearance (510(k)), De Novo classification, or premarket approval (PMA).

The FDA may also review and clear modifications to medical devices, including software as a medical device, depending on the significance or risk posed to patients of that modification.

The FDA acknowledged its traditional paradigm of medical device regulation was not fit-for-purpose for the fast-paced iterative nature of software developments and changes in general, and specifically not for adaptive artificial intelligence and machine learning technologies.

Starting in 2019, the FDA included AI in its Precertification (Pre-Cert) Pilot Program, and released a discussion paper "Proposed Regulatory Framework for Modifications to Artificial Intelligence/Machine Learning (AI/ML)-Based Software as a Medical Device (SaMD) - Discussion Paper and Request for Feedback" introducing their "Predetermined Change Control Plan (PCCP)" concept. The concept is based on a Predetermined Change Control Plan within a device's initial premarket submission, including the modifications planned by the developer, referred to as the **"Software as a Medical Device Pre-Specifications (SPS)"** and a description of the methods used to implement and control the risks of the anticipated modifications outlined by the SPS, referred to as the **"Algorithm Change Protocol (ACP)"**.

As this PCCP would be reviewed and approved during the initial submission, all future changes to the software within the scope of the approved PCCP would not require premarket review again.

Regulatory landscape in the US

In early 2021, FDA issued its "Artificial Intelligence and Machine Learning (AI/ML) Software as a Medical Device Action Plan" to summarise feedback it received on the aforementioned 2019 discussion paper outlining five key actions:

- Develop an update to the proposed regulatory framework presented in the AI/ML-based SaMD discussion paper, including through the issuance of a draft guidance on the PCCP
- Strengthen FDA's encouragement of the harmonised development of Good Machine Learning Practice (GMLP) through additional FDA participation in collaborative communities and consensus standards development efforts
- Support a patient-centred approach by continuing to host discussions on the role of transparency (including device labelling) to users of AI/ML-based devices
- Support regulatory science efforts on the development of methodology for the evaluation and improvement of machine learning algorithms including identification and elimination of bias and promoting algorithm robustness
- Advance real-world performance (RWP) pilots in coordination with stakeholders and other FDA programs to provide clarity on real-world evidence generation for AI-based software

Delivering on these key actions, in October 2021, the FDA together with Health Canada and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) jointly identified 10 guiding principles that inform the development of Good Machine Learning Practice (GMLP).

The "Good Machine Learning Practice for Medical Device Development: Guiding Principles" are intended to promote safe, effective, and high-quality medical devices that use artificial intelligence and machine learning (AI/ML) and identify areas where the International Medical Device Regulators Forum (IMDRF), international standards organisations, and other collaborative bodies could work to advance GMLP.

Regulatory landscape in the US

In April 2023 FDA issued the draft guidance "Marketing Submission Recommendations for a Predetermined Change Control Plan for Artificial Intelligence/Machine Learning (AI/ML)-Enabled Device Software Functions".

This draft guidance builds on their 2019 concept and provides recommendations on the information to be included in a PCCP provided in a marketing submission for machine learning-enabled device software functions (ML-DSF) such as the planned ML-DSF modifications, the associated methodology to implement and validate those modifications, and an assessment of the impact of those modifications. The recommendations in this guidance also apply to the device constituent part of a combination product, such as drug-device and biologic-device combination products, when the device constituent part includes an ML-DSF.

Over the past decade, the FDA has reviewed and authorised a growing number of devices legally marketed (via 510(k) clearance, granted De Novo request, or approved PMA) with ML across many different fields of medicine - the FDA provides a list of AI/ML-enabled medical devices marketed in the United States as a resource to the public about these devices and the FDA's work in this area.

The FDA's Center for Drug Evaluation and Research (CDER) has also undertaken efforts related to AI/ML for drug development, which can be found here.

AI standardisation developments

AI standardisation developments

While regulations set out what legal requirements manufacturers must meet to market products, standards provide specifications detailing how the requirements prescribed in the legal text can be met, defining concrete processes, methods, and techniques that AI providers can implement to comply with their legal obligations.

According the AIA (Article 40), harmonised standards provide operators with a presumption of conformity with the AIA. While in the EU the harmonisation of standards with the MDR and IVDR for medical devices is still ongoing, the current standards typically applicable to medical devices specifically such as **Risk Management (ISO 14971)**, **Usability (IEC 62366)**, **Quality Management Systems (ISO 13485)** and especially **Health Software (IEC 82304)** and **Medical Device Software Development Lifecycle (IEC 62304)**, as well as IT Security, together with guidance documents such as those from the MDCG or FDA, present the state-of-the-art for AI-based medical devices (albeit not outlining AI-specific requirements).

Harmonised standards with the AIA remain yet to be defined after issuance of the AIA. Such standards may focus on the high-risk requirements including Risk Management, Data Governance, Information for Users, Human Oversight, Robustness, Accuracy, Cybersecurity, Quality Management Systems and Conformity Assessments.

AI standardisation developments

The Joint Research Centre (JRC), the European Commission's science and knowledge service, has published a 2023 update of their Technical Report "AI Watch: Artificial Intelligence Standardization Landscape Update" including a National AI Strategies factsheet which provides an analysis of available IEEE standards in the context of the future European AI Regulation. The JRC concludes in their report that "several of the documents analysed have been found to provide highly relevant technical content from the point of view of the AI Act" and that "building on existing international work on AI is expected to be an efficient way to develop the standards needed for the AI Act, avoiding duplication of efforts and facilitating their broad adoption by AI providers".

ISO/IEC JTC1 SC42 is named as a primary source, and cooperation with CEN and CENELEC on AI standardisation is also suggested. Specifically, the ISO/IEC JTC1 SC42 - the first international standards committee to look at the entire AI ecosystem established in 2018 - has published several standards related to AI already, such as **"AI - Guidance on risk management"** and **"Bias in AI systems and AI aided decision making"**, with further standards under development addressing, for example, AI system lifecycle processes, functional safety, and management system or AI system impact assessment. The ISO/IEC 22989:2022 **"Information technology - Artificial intelligence - Artificial intelligence concepts and terminology"** has been made available for free here.

AI standardisation developments

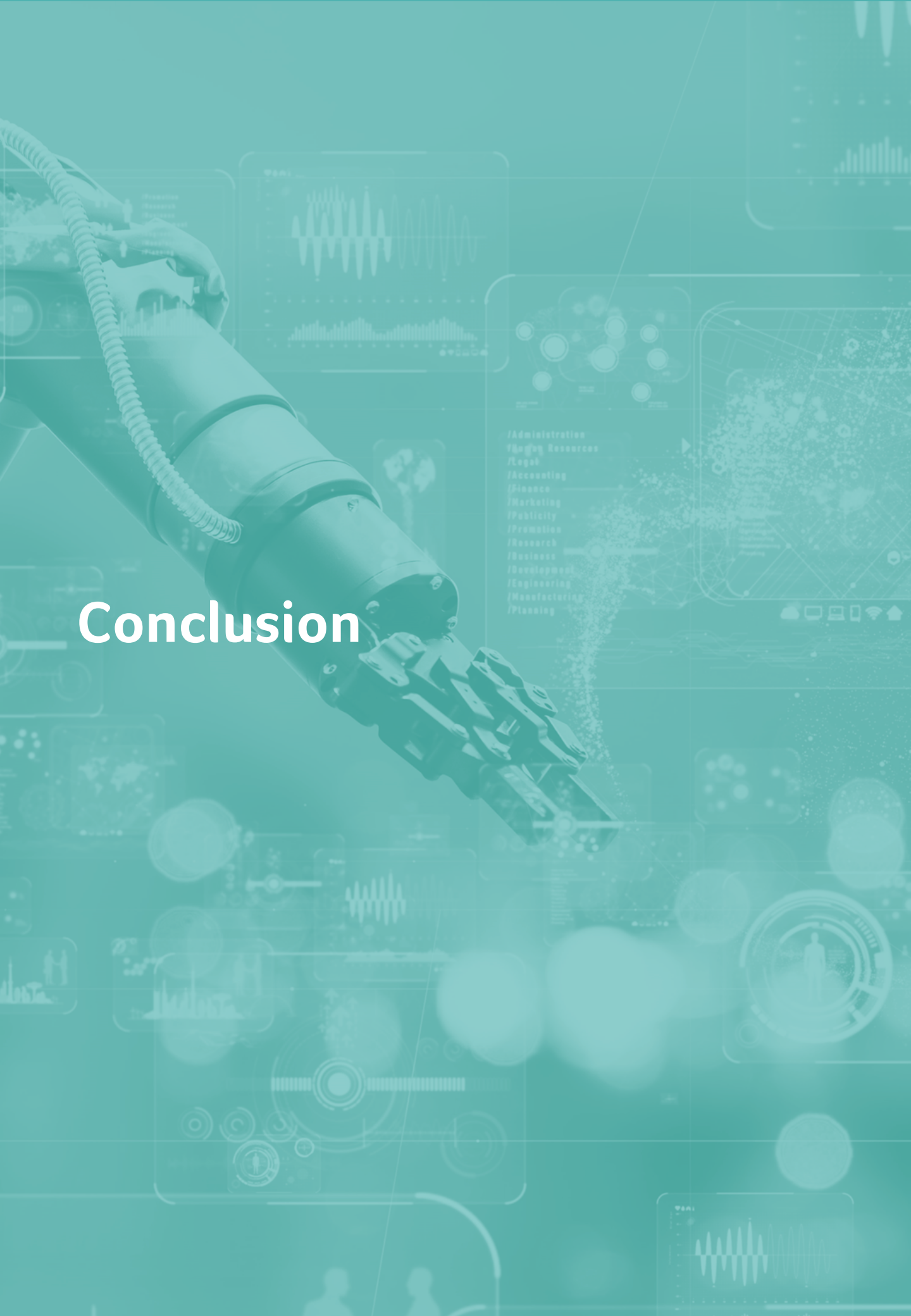
Beyond Europe, national standardisation initiatives have continually developed in many countries for several years. In **2017**, ahead of the FDA and EU Commission, South Korea's MFDS was actually first to cover AI in their "Guideline for Approval/Evaluation of Medical Device with Big Data and AI Technology Applied (guide for applicants)". China's NMPA and Japan's PMDA followed in **2018** by including an AI diagnostics (category) in their Medical Device Classification Catalog, and by issuing a review paper on "Regulatory Science on AI-based Medical Devices and Systems" respectively.

Many countries have since followed suit, issuing or updating approaches to AI-based medical devices - several of them striving for global convergence by adopting other national approaches or global harmonisation principles such as from the IMDRF.

In **January 2023**, the US-based National Institute of Standards and Technology (NIST) provided NIST AI 100-1 **"Artificial Intelligence Risk Management Framework (AI RMF 1.0)"**. While not specific to medical devices, the AI RMF is offered, together with the AI RMF Playbook, as a free resource for organisations that are designing, developing, deploying, or using AI systems to help manage the many risks of AI and promote trustworthy and responsible development and use of AI systems. The document adopts principles and terminology from, for example, other ISO/IEC standards, and provides reference to further NIS special publications related to AI.

In **April 2023**, the UK's MHRA launched an AI Standards Hub and issued their guidance "Software and Artificial Intelligence (AI) as a Medical Device", which was updated in **July 2023**. And while the FDA added the AAMI CR34971:2022 "Guidance on the Application of ISO 14971 to Artificial Intelligence and Machine Learning" to their list of recognised standards in late 2022, in 2023 the Association for the Advancement of Medical Instrumentation (AAMI), together with the British Standards Institute (BSI), published the AAMI TIR34971:2023 "Application of ISO 14971 to machine learning in artificial intelligence - Guide".

Most recently in **September 2023**, Health Canada published the draft guidance "Pre-market guidance for machine learning-enabled medical devices" which provides guidance to manufacturers who are submitting a new or amendment application for a Class II, III or IV machine learning-enabled medical device (MLMD) under the regulations.



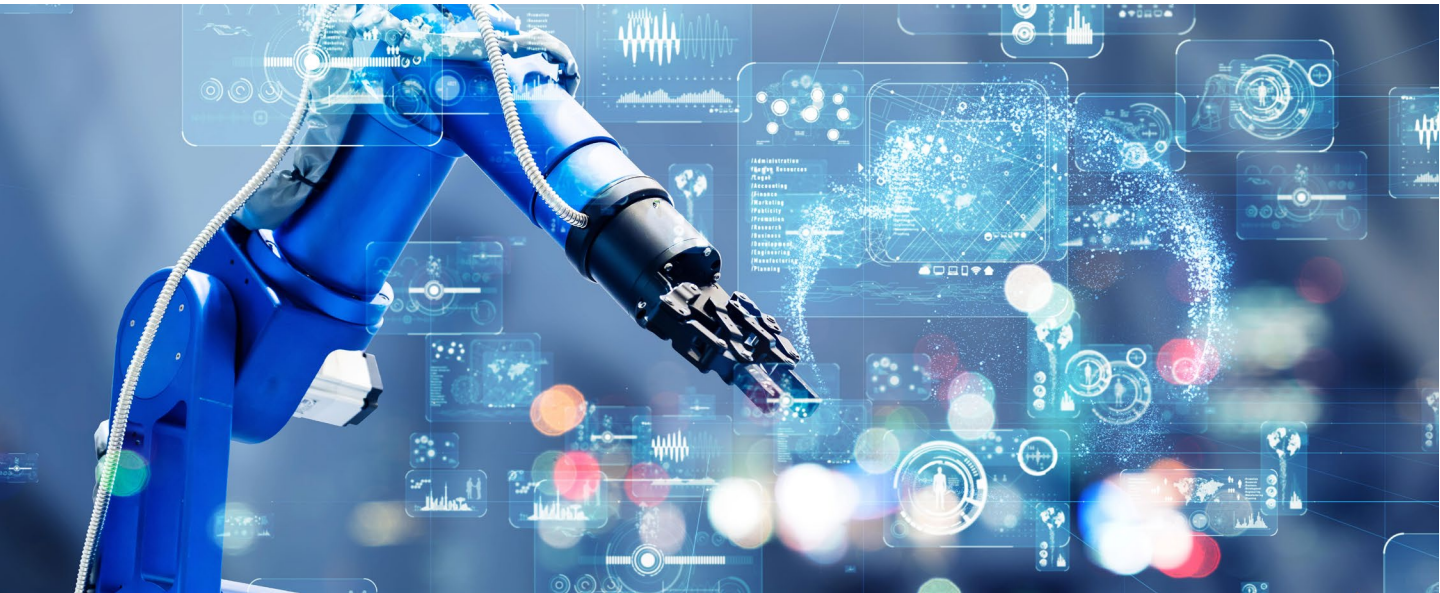
Conclusion

Conclusion

AI-enabled medical devices hold immense potential to transform healthcare by improving diagnostic accuracy, treatment outcomes, and patient care.

While the EU looks to the AIA to increase the quality of AI Systems and attempts to keep the regulatory burden proportionate, the AIA certainly adds to an already complex EU regulatory framework for medical devices when considering the MDR, IVDR, and additionally applicable regulations such as the GDPR.

AI specific requirements are evolving - however only rarely focusing on medical devices specifically, and navigating the regulatory landscape in the EU and the US still presents major challenges in terms of **clear definitions, specific regulatory and legal requirements, harmonised standards, and best practices** addressing the unique aspects of AI/ML enabled medical devices. These will all be necessary to eliminate the risks for patients posed by unsafe medical devices, and to help manufacturers avoid apparent arbitrariness in audits and approval procedures.



Congenius

Should you have an AI in medical devices challenge, please do get in touch – our Regulatory and eHealth teams are ready and happy to help.

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