Medical Devices

SECTION EDITOR

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Editorial

EMWA's medical device expert seminar series (ESS) brings together speakers with different expertise providing valuable insights into the medical device industry. With the Medical Device Regulation (MDR) in full force, experience and knowledge need to be shared, especially for unconventional medical devices. In 2023, the ESS at EMWA's conference focused on some niche medical devices. From medical writing under the MDR to medical device software, four speakers shared their experiences relevant to medical writers.

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Medical device Expert Seminar Series: Beyond traditional medical devices

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Abstract

As with every medical device expert seminar series (ESS), we learned something new at the ESS held at the EMWA Conference last May in Prague. With the Medical Device Regulation (MDR) in full swing, the speakers not only discussed MDR-compliance challenges but also shed light on niche products, such as in vitro diagnostics (IVDs), combination products, and medical device software (MDSW). With great pleasure, we summarise the key messages of each of the four presentations for our readers.

Medical writing and the MDR

Our first speaker, Tom Melvin, a medical doctor-turned-regulator-turned-academic, opened the session with a brief discussion of the MDR changes and its effects on the current public health situation, including the impact on medical writers. Currently Associate Professor of Medical Device Regulatory Affairs at Trinity College Dublin, Tom worked for 7 years as a senior medical officer in medical devices at the Health Products Regulatory Authority.

The presentation began with a brief history of MDR developments from when the Medical Device Directive (MDD) was put in place in 1993 to the current state. With more than 33,000 medical technology companies in Europe[1], of which 95% are small- and medium-sized, it's evident who's taking the brunt of the transition hurdles. Though the EU MDR was necessary to update the outdated directive, the challenges of its implementation are affecting the cost and predictability of compliance requirements, and ultimately, the availability of the products in the EU market. But it wasn't until October 2021 when the regulators first became aware of the risk of product unavailability, especially for high-risk devices whose certificates would expire in May 2024.

> In December 2022, a clear proposal was made to amend the transition period for medical devices to curtail the risk of impending shortages.

So finally, the system had to grant more time, and in December 2022, a clear proposal was made to amend the transition period for medical devices to curtail the risk of impending shortages. But when the resulting amendments to the EU MDR were released under Regulation (EU) 2023/607 in March 2023, the industry was sent scrambling to understand the slew of conditions in the

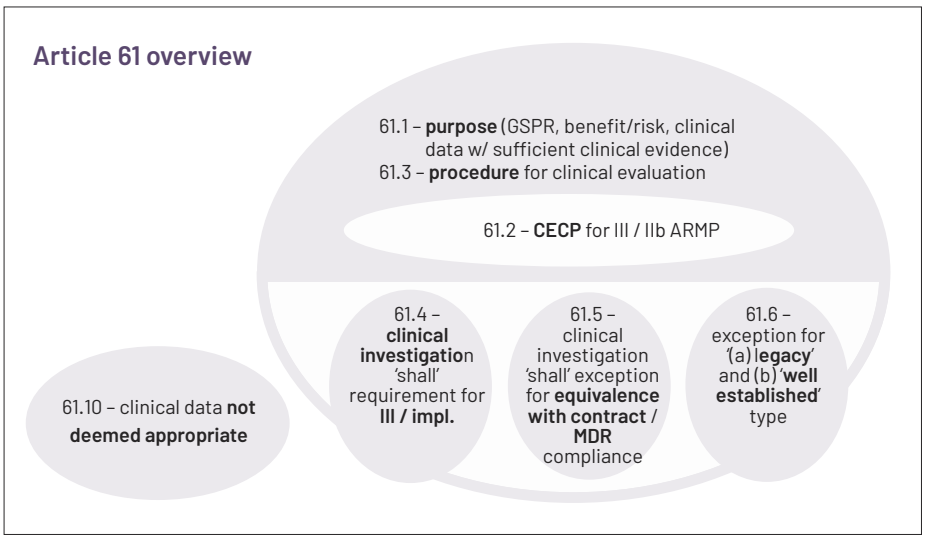

Figure 1. MDR article 61 overview

Figure by Tom Melvin, used with permission.

Abbreviations: GSPR, General Safety and Performance Requirements; CECP, Clinical Evaluation Consultation Procedure; MDR, Medical Device Regulations; ARMP, Administer and/or remove a medicinal product; impl, implantable device.

qualification of devices for the extended timelines. Many questions remain, and the situation continues to unfold before us. Despite the many factors affecting the moving timelines for compliance, medical writers are still best equipped to understand the writing implications from the regulation.

In a recap of Article 61 (see Figure 1), a graphic interpretation of the regulation illustrates different pathways applicable to different risk classes and the respective clinical investigation requirements.

Of particular importance is additional information pertaining to clinical evaluation as well as expectations for legacy devices and the limitations of declaring equivalence, found in the ISO 14155 (GCP)[2], MDCG 2021-6[3], and MDCG 2021-8[4]. And lest we forget, specific country regulations need to be considered too. But finally, a short mention of the European Database for Medical Devices (EUDAMED) objectives is a subtle reminder to stay optimistic about the efforts towards harmonisation across Europe.

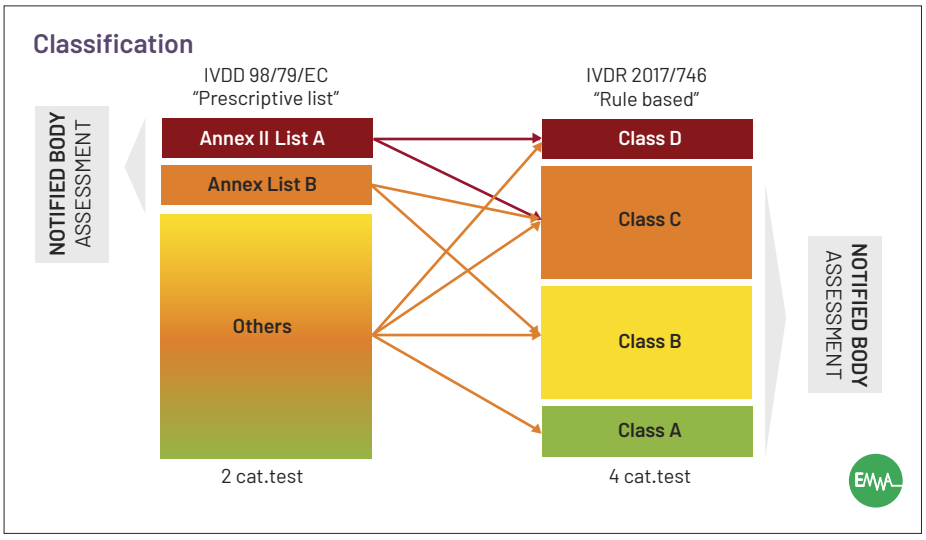

Figure 2. Classification under the IVDD and IVD6

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Abbreviations: IVDD, Invitro Diagnostic Directive; IVDR, In Vitro Diagnostic Regulation.

Another development includes the Co-ordinating Research and Evidence for Medical Devices (CORE-MD), a work package under European Union Horizon 2020, examining the number of ISOs with clinical evidence requirements. But with all the ongoing efforts, perhaps something to look forward to most for regulatory writers are the developments toward standardising clinical evaluation through a yet-to-be-released ISO 18969.

In Vitro Diagnostic Regulation (IVDR) in the context of clinical trials

The second presentation of the hour was delivered by IVD regulatory expert and trainer Anne Paulussen for Qarad in Belgium, a consulting company specialised in regulatory affairs and quality systems for IVD and medical devices. Having worked more than 10 years in the pharmaceutical and medical industries, in both development and post-marketing activities, Anne is now involved in training and educating IVD developers in understanding the new regulations.

Like the MDR, the In Vitro Diagnostic Regulation (IVDR) was a much-needed reform to the outdated In Vitro Diagnostic Directive (IVDD, 98/79/EC) of 1998. What was once based on a "prescriptive list" of devices in the IVDD, wherein the majority of IVDs were self-certified and had easy access to the EU market, the classification under the IVDR is based on risk-based rules (Figure 2). Now under the IVDR, the majority of these "other" IVDs that did not fall under the List A or List B of Annex II of the IVDD require Notified Body (NB) approval and more complex and costly approaches to provide clinical evidence.

> But which assays are considered IVDs in clinical trials?

And just like the adjustments for the MDR timelines, under the conditions drawn out in the Regulation (EU) 2023/607 amendment, the timelines for the IVDR had to be adjusted too, to give industry more (much needed) time to comply.

Meanwhile, manufacturers must continue completing their technical documentation and ensuring the robustness of clinical evidence to support the performance claims of the IVD. But which assays are considered IVDs in clinical trials?

Typically, assays in clinical trials have different purposes and development histories. And the questions that need to be asked impact the ruling for conducting the clinical trial. In a simplified example taken from MDCG 2022-10,[5] the processes are categorised into those "with" or

"without" impact on the patient management, thus determining whether the process must comply with the IVDR. Specifically, for processes without an impact on patient management, like those pertaining to stratification and data analysis endpoints, the IVDR does not apply. And for processes with impact on patient management, like patient selection and monitoring, the IVDR clearly applies.

However, if the answer is yes to the following speculative condition, "Is it predictable that the assay will be used with impact on patient management in future clinical trials?" then IVDR (Annex I) also applies!

In the context of clinical trials, the IVDR regulates only the development and manufacture of IVDs, not their use. Thus, if the IVD is used outside the intended purpose, the clinical trial sponsor assumes the obligations of manufacturers under Article 16(1) of the IVDR. The sponsor is also responsible for other products used in the trial and must document the competence of the testing laboratories to support the reliability of the results.

For companion diagnostic (CDx), an IVD used to identify patients and essential to qualifying them for the safe and effective use of a specific medicinal product, additional considerations must be made as additional time is required for the consultation process when the NB must seek the scientific opinion of the European Medicines Agency (EMA) during a CDx review. But with limited NB availability, it is no surprise that as of May 2023, only one CDx has been approved under the IVDR.

Not only do pharmaceutical sponsors and IVD manufacturers deal with different products, but they also function and represent two worlds apart. The timelines for developing an IVD are vastly different to that of a drug product, and so are the regulations. And where does the medical writer lie in this clash of two worlds? Perhaps speaking both regulatory languages of the pharmaceutical and IVD industries is a good place to start.

Combined products: regulation and clinical development

Another type of medical product that must take into consideration the regulations for pharmaceutical products as well as medical devices are combined products, combination products, or drug device combinations. Guest speaker Kathy Wang, the Regulatory Affairs Director, Devices and Digital Therapeutical, at AstraZeneca, discussed navigating regulatory pathways in various regions and how to bridge the gap

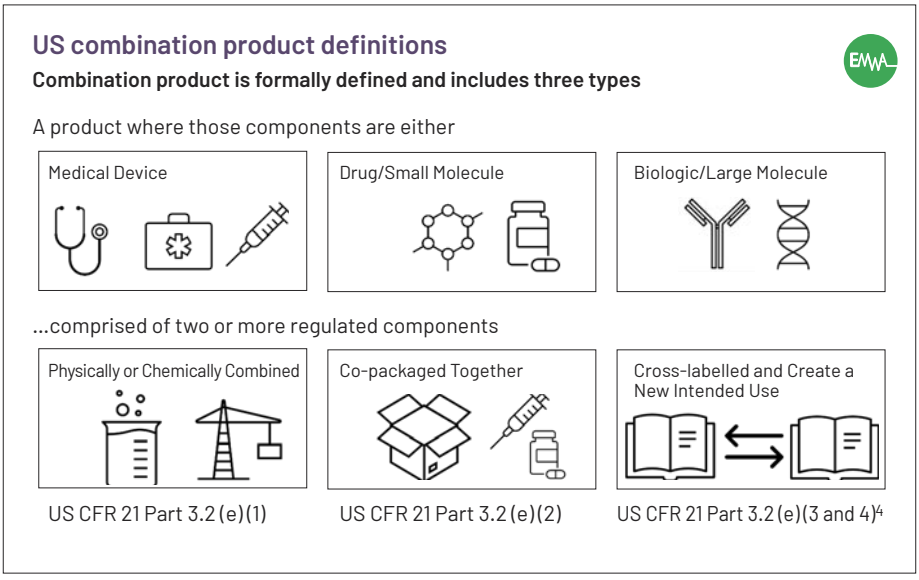

Figure 3. US combination product definitions

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Abbreviations: US CFR, United States Code of Federal Regulations.

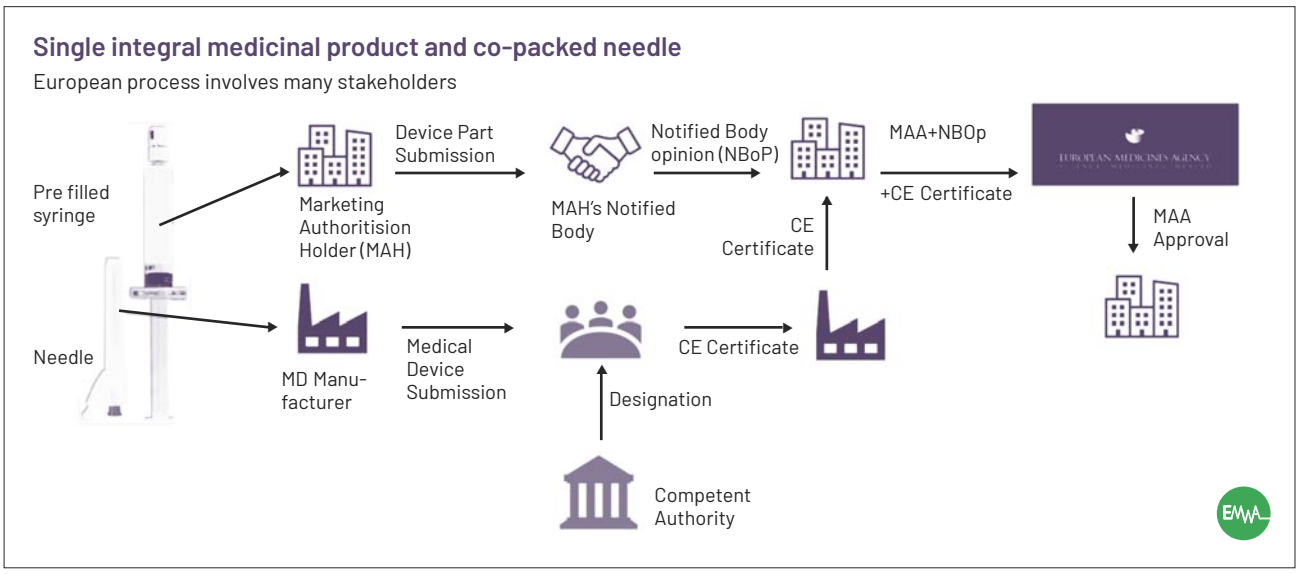

Figure 4. Complex process of MAA approval in the EU
Figure by Kathy Wang, used with permission.

between the medicinal products and the medical device frameworks.

Kathy's presentation began with an overview of these types of products and how they are regulated in the United States (US) and in the EU. Despite the development and increasing use of combination products, medical devices, and digital health technologies, there is no harmonised regulatory framework for these products globally. In the US, combination products are formally defined and categorised in the US regulations (see Figure 3), resulting in a streamlined approach to pre-market submissions and post-market activities.

If coordinating the application is not challenging enough, manufacturers must consider the different timelines of drug (for e.g., 10 to 15 years) and device (for e.g., 2 to 5 years)

From a submission perspective, the US FDA center responsible for reviewing the entire submission is determined by the combination product's primary mode of action (PMoA). For example, the submission dossier for a combination product with a drug PMoA, like a single-integral medicinal product and co-packed needle, will be a drug submission to the Center for Drug Evaluation Research with device information integrated into Module 3 of the eCTD (Electronic Common Technical Documentation). And for combination products with a device PMoA, the drug information is included in the pre-market notification or application to the Center for Devices and Radiological Health.

By comparison, in the EU, there is no formal recognition of the term "combination product" or the different types established in the US (see Figure 3); however, products that combine a drug with a device are referred to as drug-device combinations and involve more than just one regulatory authority. Therefore, the final market authorisation application would not only require device information but also an NB opinion or conformity declaration for the device component (see Figure 4).

And if coordinating the application is not challenging enough, manufacturers must consider the different timelines of drug (for e.g., 10 to 15 years) and device (for e.g., 2 to 5 years) development and the different types of clinical

Clinical documentation – Combined trials and the role of a medical writer

Medicinal Product Documentation	Overlap Potential	Medicinal Device Documentation
Clinical Trial Application		Clinical Investigation Application
		Clinical Evaluation Plan
Clinical Trial Protocol	◀ Protocol ▶	Clinical Investigation Plan
Medicinal Product IB	◀ Investigator Brochure ▶	Medical Device IB
Clinical Study Report	◀ Study Report ▶	Clinical Investigation Report
Clinical Summaries (Overview as part of the CTD)		Clinical Evaluation Report (Part of technical file, updated regulatory)

Figure 5. Clinical documentation for drug-device combinations
Figure by Kathy Wang, used with permission.

evidence needed for each component.

And as Kathy emphasised in her talk, for the medical writer, being able to understand the overlap potential of the clinical documents required for a combination product or drug-device combination would be an invaluable asset (see Figure 5).

Regulating medical device software

Just like the unique challenges faced by IVDs and drug-device combinations, devices such as Medical Device Software (MDSW) or Software as Medical Devices (SaMD) must take into consideration special regulations.

Our speaker on MDSW was Dragan Jovic, a medical software consultant and certified auditor, currently the Director of Quality Assurance and IT for Re5 ApS, a medtech company based in Denmark specialising in neurological treatments.

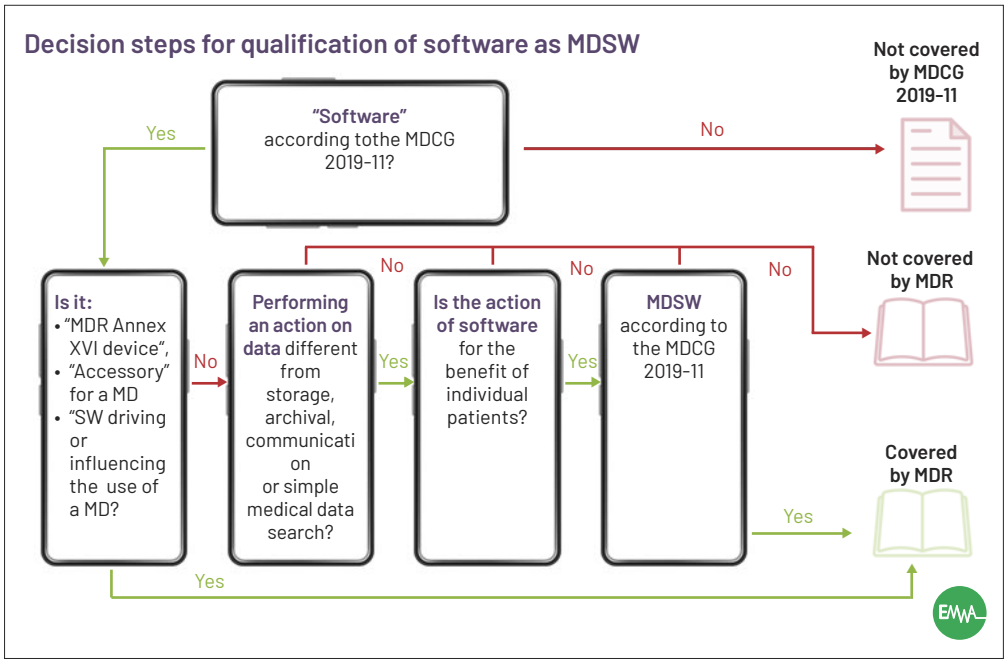

Figure 6. Decision steps for qualification of MDSW

Figure by Dragan Jovic, used with permission.

Abbreviations: MDCG, Medical Device; MDR, Medical Device Regulation; MD, Medical Device; SW, Software; MDSW, Medical Device Software.

Under the MDR, changes to the classification of software have been a leading cause for concern. The term MDSW was established in the EU within MDCG 2019-11[7] and falls under the definition of a medical device according to MDR Article 2(1). On the other hand, the term SaMD was established by the International Medical Device Regulatory Forum (IMDRF) to refer to software apart from the hardware medical device. Thus, understanding when software is a medical device is key, and this must take into consideration the EU MDR Rule 11 of Annex VIII, or all classification and implementing rules of Annex VIII of the IVDR (see Figures 6 and 7).

In addition, manufacturers need to follow relevant standards such as IEC 623041(11), which lays out a best practices framework for software development including cybersecurity management and the corresponding documentation based on the software safety classification. Moreover, the release of MDCG 2020-1 for clinical evaluation of a MDSW lays out the definition for clinical benefit and clinical evidence for SaMDs or MDSW. When the software is designed to drive or influence another medical device, the necessary compliance requirements are assessed within the intended purpose of the driven device and not the MDSW.

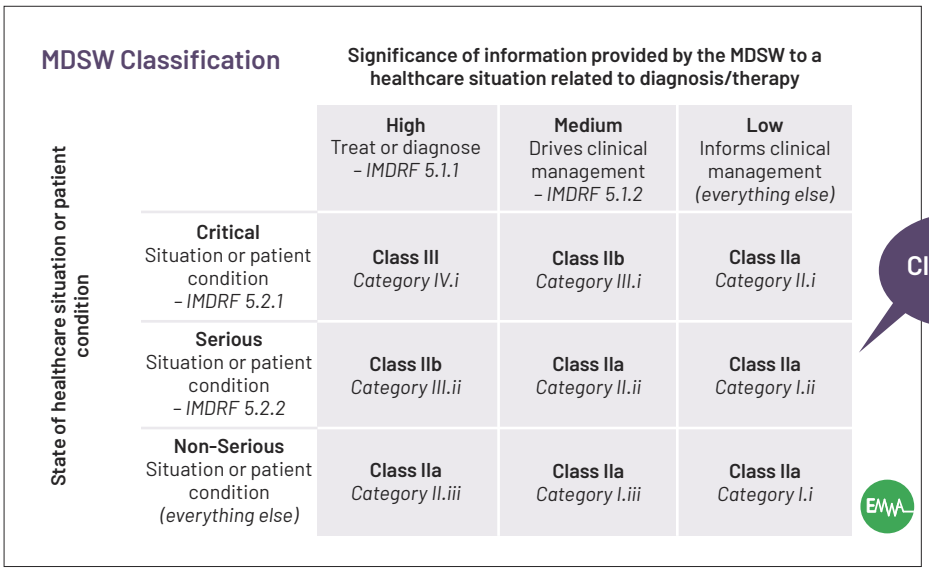

Figure 7. Classification of MDSW

From MDCG Guidance 2019-11

Abbreviation: IMDRF, International Medical Device Regulator's Forum.

But as much as MDSW may further innovate the practice of healthcare, it is not unusual for manufacturers to create the MDSW before having any documentation of its development and try to avoid regulatory processes for their software. Sometimes medical application developers have little or no formal medical training and do not involve physicians in the process. Sometimes developers may even forget the medical purpose while defining the intended purpose of their device. Such communication gaps may be an opportunity for medical writers to apply their skills to provide documentation and clarity in the regulatory processes for SaMDs and MDSWs.

Conclusion

With all this knowledge shared, the panel discussion covered topics ranging from the benefit-risk assessment to the role of medical writers in this evolving regulatory landscape. Both the speakers and the audience agreed that a more transparent communication among

medical writers would be needed to share best practices and experiences. The goal is the same for all: patient safety!

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Disclaimers

The opinions expressed in this article are the author's own and not necessarily shared by her employer or EMWA.

Disclosures and conflicts of interest

The author declares no conflicts of interest.

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