MEDTECH & PHARMA PLATFORM

Interface between the EU MDR, IVDR and CTR:

Challenges in conducting clinical trials involving medicinal products with medical devices or IVDs

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Overview

In the EU/EEA, clinical trials involving both medicinal products and devices are regulated under different regulatory frameworks. This position paper focuses on clinical trials involving medicinal products and medical devices / *in vitro* diagnostics (IVDs) (hereafter referred to as 'devices') and highlights some of the challenges encountered by actors conducting such trials when navigating the applicable legal frameworks.

Applicable legislation includes the Clinical Trials Regulation (CTR, 536/2014), the Medical Devices Regulation (MDR, 2017/745), the *In Vitro* Diagnostics Regulation (IVDR, 2017/746), and applicable national legislation. Certificates obtained under the Medical Devices Directive (MDD, 93/42/EEC) or the *In Vitro* Diagnostics Directive (IVDD, 98/79/EEC) remain valid until 2026 to 2028, depending on the type of device, under the conditions set in the Regulations as amended by Regulation (EU) 2023/607. These regulations and applicable directives set detailed requirements for the products and processes under their scope and their coexistence creates challenges for actors involved in clinical trials.

Use of devices in clinical trials

Devices can be used in a clinical trial involving a medicinal product for several purposes, including the preparation or delivery of medicinal products, monitoring or measuring parameters, collecting data, and providing information for diagnostic purposes.

This paper focuses on trials which simultaneously investigate a medicinal product and a device (hereafter referred to as 'combined trials'). Specifically, this paper covers the following cases of combined trials, which can evaluate both CE-marked and non-CE-marked devices:

- CE-marked devices used within their intended purpose,
- CE-marked devices not used within their intended purpose or devices which are not yet CE marked and for which the trials/investigation is used for the conformity procedure,
- Devices which are not to be CE marked, such as custom-made devices and devices falling under the in-house exemption for health institutions.

Challenges for combined trials

There is currently no specific EU procedure for combined trials. In this context and with the exception of integral drug-device combination products, clinical trials sponsors are required to prepare and submit two separate applications, one according to the CTR for the medicinal product, through the Clinical Trials Information System (CTIS), and one according to the MDR / IVDR for the device subject to the clinical investigation/performance study, through national databases until the European Database on Medical Devices (EUDAMED) is functional (mandatory use planned for Q4 2024).

1. Obligations of various actors

Combined trials include medicinal products as well as devices, which are most of the time developed/provided by different organizations, fall under CTR/Medicinal Products Directive (MPD, 2001/83/EC) and devices under the MDR / IVDR. The lack of guidance detailing the roles and

responsibilities of involved parties leads to further complexity, diverging interpretations of each party's responsibilities and thus divergent expectations. These poses challenges, particularly in cases where sponsors file applications for early phase medicinal product development activities, such as Phase I clinical trials, that use a device that is not CE-marked. In such cases, it can be challenging for the device manufacturer to compile the document necessary to conduct, in parallel, the required performance study as the drug trial is small and there is no guarantee that the medical device will be included in larger studies or subject to a marketing application.

2. Absence of common procedure

The obligation for sponsors of combined trials to submit two separate applications presents an inherent challenge, adding to an already demanding application process. Currently, the application for a clinical investigation or performance study should ideally be submitted before the CTR application so that the sponsor has all the information required for the medicinal product's clinical trial application, or at least in parallel.

3. EUDAMED

As defined in the legislation, EUDAMED must be fully interoperable with the CTR. Until it is achieved, sponsors must submit applications and fulfil post-market obligations via national authorities. This creates an additional burden for sponsors, especially in the case of multinational trials for which as many applications as there are Member States involved in the trial must be submitted.

4. Coordination among National Competent Authorities

Sponsors of combined trials, especially when using IVDs, are experiencing inconsistencies with regard to the interpretation and implementation of the IVDR on submission processes and the timing of performance study applications relative to clinical trial applications under the CTR across EU Member States. The lack of coordination and guidance for the assessment of clinical investigation and performance evaluation applications in Member States creates hurdles for sponsors.

5. The role of central laboratories

Central laboratories, which operate in a highly regulated environment, analyze patient samples from clinical trials and utilize novel testing methods for which there are no other commercially viable options. A significant number of IVDs used in clinical trials in the EU are developed and used by central laboratories. In this context, it would be beneficial to clarify the definition of "health institution" under the IVDR, and especially whether central laboratories can be considered as falling under this definition.

Conclusion

The challenges listed in this paper and the absence of a common procedure creates a hurdle for organizations that wish to conduct combined trials, disincentivizing such trials in Europe. The issue is especially salient for smaller companies that have limited resources.

Therefore, the MPP Association is calling for:

- Guidance to provide legal certainty for all actors to facilitate review and approval of combined trials,
- Common application process for combined trials in the EU,
- Faster deployment of EUDAMED,
- Improved coordination among Member States in their assessment of device applications in the context of clinical trials, and
- Guidance to clarify the status of central laboratories.

The MPP Association urges all involved stakeholders to engage in discussions with a view to creating an appropriate framework for combined trials and accelerating patients' access to safe and innovative health technologies in Europe.

About the Medtech & Pharma Platform Association

The Medtech & Pharma Platform Association (MPP) brings together companies from the pharmaceutical, medtech, and tech sectors and provides opportunities to exchange knowledge and to collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech, and tech industries,
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options,
- To work toward the development of a balanced and proportionate regulatory and policy framework for combined products including connected combined products.