Developing Robust Submission Strategies for Combined Studies

Medical interventions increasingly involve the use of technology and devices. New treatments may involve a medical device, combination product or *in vitro* diagnostic device. For sponsors this means their studies have additional regulatory requirements to meet, each on very distinct submission pathways. The assessment of the safety or performance of the device is not in scope, but the device is necessary to conduct the study. Clinical trials with human subjects where such devices are deployed must comply with applicable regulations EU CTR (Regulation (EU) 536/2014), MDR (Regulation (EU) 2017/745) and/or IVDR (Regulation (EU) 2017/746).

Identifying and managing the additional regulatory requirements for these studies can be confusing. Multiple factors must be considered, such as whether the device is CE-marked, is being used outside of its intended purpose or is custom-made. The submissions process may be further complicated by additional national regulatory and ethical requirements.

Even where there is some overlap with the study documentation, the additional device-specific regulations require extra time, effort and expertise. Missing information or a misfiled application can negatively impact a study timeline. Planning a route through the labyrinth of regulations can avoid these delays. Time dedicated to building a robust EU submission strategy in advance means time saved later on in the submissions process.

Conformity Assessment of Medical Devices and *in Vitro* Diagnostic Devices

In the EU, the device manufacturer is responsible for complying with and demonstrating safety standards. Medical devices do not require official authorisation from a public agency in the EU, unlike medicinal products. However, they need a conformity assessment procedure. Devices that meet EU requirements bear the CE mark upon market entry. Conformity assessment procedures vary according to the devices' risk classes. High risk devices have greater regulatory oversight than low risk devices. The rules for risk classification of devices are listed in Annex VIII of MDR and IVDR and in the corresponding Medical Device Coordination Group (MDCG) guidance documents including MDCG 2021–24 and 2020–16.

For low-risk devices, with some exceptions, the manufacturer can conduct the conformity assessment procedure themselves and issue the EU Declaration of Conformity. Higher risk devices require an independent conformity assessment procedure by a notified body (NB). These conformity assessment procedures can consist of one or more modules, depending on the risk characteristics. The modules concern the manufacturer's quality management system, the product's technical documentation, the individual type-examination, production quality assurance or conformity to an EU type-examination. Typically, the process includes an audit of the manufacturer's quality system. NBs must consult specific expert panels before granting a Certificate of Conformity for some high-risk devices. Certificates of Conformity are valid for the period indicated and shall not exceed five years. Manufacturers can request an extension of validity for further periods (less than five years). A re-assessment of conformity must be conducted as part of the extension request.

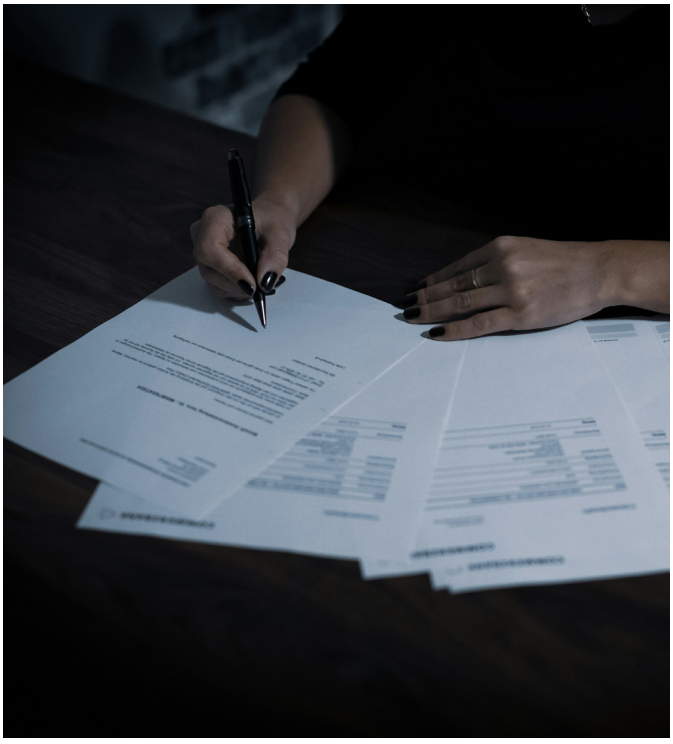
Medical devices and IVDs certified under Medical Device Directive (MDD), Active Implantable Medical Device Directive (AIMDD) or *In Vitro* Device Directive (IVDD) should undergo a conformity assessment procedure under the new regulations. These assessments must be carried out before the end of the transitional periods stipulated by MDR and IVDR. The large number of MDs and IVDs that must undergo new conformity assessments has exceeded the capacity of NBs. This has led to several extensions of the transitional periods.

Drug-device Combination Products (DDC)

The multipurpose nature of drug-device combination products has blurred their definitions depending on the applicable regulations. In July 2021 the EMA published the Guideline on Quality Documentation of Medicinal Products when Used with a Medical Device. The guidelines define three types of combination products as medicinal products.

1. Integral DDCs: the medical device and/or device part and the medicinal product form an integral product that is not reusable and where the action of the medicinal product is principal. Example: a single-use dry powder inhaler preassembled with the medicinal product. It is ready for use but cannot be refilled when all doses are exhausted.

2. Co-packed DDCs: the medical device is packed (or packaged) together with the medicinal product. Example: Reusable dry powder inhaler packed with dry powder capsules.



3. Referenced DDCs: the product information refers to a specific medical device to be used with the medicinal product, and the medical device is obtained separately by the user of the medicinal product. Example: Reusable dry powder inhaler and dry powder capsules packed separately but the patient information leaflet indicates that the capsules can only be used with a specific inhaler.

Article 117 of the MDR requires a NB to provide an opinion on the conformity of the DDC against MDR Annex I. Devices already CE-marked do not require an opinion on conformity.

Tips for Creating Robust Submission Strategies:

1. **Seek Submission Route Clarity:**
   Clarify the regulatory requirements of the various regulatory authorities (RAs) before mapping your study's submission route. There may be country-specific requirements in addition to EU regulatory requirements.

2. **Develop a Plan for Updating Documents:**
   Where additional country-specific requirements apply, find a way to add these considerations to the overlapping documentation for other RAs.

3. **Map a Regulatory Pathway with Clear Timelines for each Requirement:**
   Agree internal deadlines for drafting and reviewing documentation. Define the roles and responsibilities for document preparation and the processes to follow. The device manufacturer may need to be involved in the regulatory process as well as the sponsor.

4. **Anticipate Potential Questions and Provide Relevant Information Upfront:**
   It may be prudent to create an accompanying cover letter with additional supplementary details. This could include descriptions of the roles of investigation sites and central testing sites and other relevant information about patient recruitment and enrolment. By providing these supporting materials sponsors can minimise the number of potential validation questions from each RA.

Conclusion

While the regulatory route is convoluted, it is not impassable. Having a robust strategy in place from the outset ensures that sponsors take the most direct route, avoiding wrong turns, dead ends and delays.

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Vesta Marciulioniene, Director Regulatory Affairs at ICON, has spent more than a decade at Pfizer and a decade at Covance & Labcorp. She has extensive clinical research expertise with a strong focus in start-up, having formerly taken global roles of Head of Start Up Centre of Excellence and Head of Site ID in previous organisations. Vesta has been leading multifunctional teams regionally and globally, aiming to connect the start-up and regulatory world with clinical project delivery.