Whitepaper

Combination Products in the EU MDR era

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With the introduction of the MDR 2017/745 the regulation of combination products should become clearer but at the same time has become also more complicated. Article 117 of the MDR provides the framework for regulating the different parts of a combination product, including the medicinal part of the product. Therefore Directive 2001/83/EC is also amended with similar requirements.

If the principle intended action of the combination product is achieved by the medicine, the entire product is regulated as a medicinal product under Directive 2001/83/EC or Regulation (EC) No 726/2004.

If the principle intended action is achieved by the device part, then the product is regulated by the MDR 2017/745.

Combination products can be divided into two types of combination products:

1. Integral: the medicinal product and device form a single integrated product e.g. pre-filled syringes and pens, patches for transdermal drug delivery and pre-filled inhalers;

Examples of medical devices in integral DDCs are:

- Devices for delivery to site of action e.g. the dropper on the top of the container with eye drops or the mouthpiece on the top of spray cans for throat sprays.
- Single dose pre-filled syringes, pens and injectors.
- Multi-dose pens and injectors containing a pre-filled cartridge, where the cartridge cannot be replaced and the pen is not designed for subsequent use with a new cartridge.
- Drug-releasing intra-uterine devices; pre-assembled, non-reusable applicators for vaginal tablets.
- Dry powder inhalers that are assembled with the medicinal component and ready for use with single or multiple doses, but cannot be refilled when all doses are taken.
- Implants containing medicinal products whose primary purpose is to release the medicinal product.
- Medicinal products with an embedded sensor.

2. Co-packaged: the medicinal product and the device are separate items contained in the same pack e.g. reusable pen for insulin cartridges, tablet delivery system with controller for pain management.

Examples of medical devices in non-integral DDCs are:

- Oral administration devices (e.g. cups, spoons, syringes)
- Injection needles and filter needles
- Refillable pens and injectors (e.g. using cartridges)

- Reusable dry powder inhalers, spacers for inhalation sprays
- Nebulisers, vaporisers
- Pumps for medicinal product delivery
- Electronic tablet dispensers

Medical devices that are co-packaged or obtained separately must be CE marked in accordance with the medical device legislation.

Article 117 of the MDR introduced a new requirement for medicines with an integral device. A CE certificate for the device should be included in the marketing authorisation application. If it is not CE marked it would need to be certified, if marketed separately. Therefore, the applicant must include an opinion from a Notified Body on the conformity of the device. This requirement does not apply to Class I devices (non-sterile, non-measuring).

For new marketing authorization applications, a Declaration of Conformity or CE Mark will be required for the device component of a drug-device combination product. This is in order to determine whether the device component meets the MDR requirements established in Annex I of the Regulation or not. If a CE mark or DoC cannot be provided, an opinion from a Notified Body supporting conformity to Annex I rules, must be provided.

Drug-device combination products currently authorized under the Medical Device Directive 93/42 or authorized before the MDR implementation date of 26 May 2021, will not be impacted by MDR Article 117 requirements. However, such products may become subject to MDR Article 117 requirements if manufacturers make substantial changes to, replace or add device components to their products.

Role of EMA

EMA is responsible for evaluating the quality, safety and efficacy of marketing authorisation applications assessed through the centralised procedure, including the safety and performance of the medical device in relation to its use with the medicinal product.

EMA released a draft guideline on quality requirements for regulatory submissions for medicines that include a medical device (drug-device combinations). The device can be integral, co-packaged or obtained separately.

- Quality requirements for drug-device combinations

The guideline clarifies expectations laid down in Directive 2001/83/EC and addresses the new obligations in the MDR, in particular the requirements under Article 117.

The related Q&A document has not been updated since October 2019 and consultation of the guideline was closed in August 2019. It is EMA's intention to finalise the guideline before the implementation date of the MDR.

Medical devices with an ancillary medicinal substance

Medical devices containing an ancillary medicinal substance to support the proper functioning of the device fall under the medical devices legislation and must be CE marked.

Examples of these kind of products are drug-eluting stents, bone cement containing an antibiotic, catheters coated with heparin or an antibiotic agent and condoms coated with spermicides.

Role of EMA

The Notified Body must seek a scientific opinion from EMA on the quality and safety of the ancillary substance if it is derived from human blood or human plasma, or if it is within the scope of the centralised procedure for the authorisation of medicines.

For other substances, the Notified Body can seek the opinion from a national competent authority or EMA.

EMA publishes Consultation procedure Public Assessment Reports (CPAR) on its scientific opinions.

Companion diagnostics ('in-vitro diagnostics')

With the introduction of the In-Vitro Diagnostic Devices Regulation a new classification system for the obligation to undergo a conformity assessment by a Notified Body is required.

Role of EMA

The Notified Body must seek a scientific opinion from EMA on the quality, safety and suitability of the companion diagnostic to the medicinal product concerned, if:

- the medicinal product falls exclusively within the scope of the centralised procedure for the authorisation of medicines, or
- the medicinal product is already authorised through the centralised procedure, or
- a marketing authorisation application for the medicinal product has been submitted through the centralised procedure.

For other substances, the Notified Body can seek the opinion from a national competent authority or EMA.

Further information on the consultation procedure between the Notified Body and a competent authority or EMA will be provided.

Conclusion

With the introduction of the MDR 2017/745 and IVDR 2017/746, the amendment of the Pharmaceutical Directive 2001/83/EC and the additional guidance from EMA the treatment of combination products from regulatory perspective has become clearer. In principle a clear process on the cooperation of the Notified Bodies and EMA or National Authorities is presented. A lot of new questions are raised with the implementation and it is certain that additional guidance's by Authorities need to be provided. As with new processes the amount of hick ups and how they are dealt with, will tell if the implementation of the new Device directives, amendment of the Pharm Directive and cooperation of Notified Bodies and EMA/National Authorities will be successful and provide better performing and safer combination products for patients.

If you would like to understand more about this subject please check our website Starodub.nl or contact us at info@starodub.nl.

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About the Author

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Bringing regulatory knowledge on Medical Devices and combination products is my expertise. I am trained in Quality Management, GxP, Risk Management and Auditing. I author and review medical device technical documentation. I support clients with quality processes and Management Reviews. Clients value my input as being of high quality and they appreciate the open communication and collaborative approach in projects.

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