

EBE-EFPIA Position Paper

An Industry Perspective on Article 117 of the EU Medical Device Regulation: Labelling Requirements for Prefilled, Non-Reusable, Integral Drug-Delivery Device Combination Products

Date: 8 August 2019

Executive summary

Prefilled, non-reusable, integral drug-device combinations (DDCs) are regulated as medicinal products, if the intention is to administer the medicinal product to the patient. However, the device component needs to conform with “relevant” General Safety and Performance Requirements set out in Annex I of the Medical Device Regulation (MDR, Regulation (EU) 2017/745).

It is EBE and EFPIA’s views that for non-reusable, integral drug-device combination products, the labelling requirements for medicinal products take precedence over labelling requirements for medical devices. As a pragmatic approach, a Notified Body’s review of the “Instructions for Use” for the device component could be in the scope of the assessment by the Notified Body for the delivery of the Notified Body’s opinion. In addition, EBE and EFPIA recommend special considerations be given to complex innovative DDCs, use of international symbols and CMR (carcinogenic, mutagenic or toxic to reproduction) and endocrine-disrupting substances.

Unless clarification is obtained now, there is a risk for conflicting and overlapping labelling requirements, with the coming into force of the MDR, as of 26 May 2020.

This paper considers these technical and procedural concerns and challenges being discussed amongst Industry, with a view that recommendations made are taken into consideration as guidance and implementing acts related to integral drug-device combination products get published.



Problem statement

Unless clarified now, there is a risk for conflicting and overlapping labelling requirements, with the entry into force of the MDR, as of 26 May 2020.

Prefilled, non-reusable, integral, drug-device combinations intended to administer a medicinal product (here referred to as DDCs) are regulated as medicinal products (Directive 2001/83/EC). However, the device component needs to conform with “relevant” General Safety and Performance Requirements set out in Annex I of the Medical Device Regulation (MDR, Regulation (EU) 2017/745).

Annex I (*‘General Safety and Performance Requirements’, GSPRs*) of the new Medical Device Regulation (EU) 2017/745 (MDR) contains extensive labelling requirements for medical devices. In the absence of an explicit confirmation that labelling requirements for medicinal products take precedence, there is an obvious risk for different interpretations between Sponsors, Health Authorities and Notified Bodies (NBs).

If divergent (and redundant) approaches to the labelling of DDCs are taken, the clarity of the product information will suffer. That is not in the interest of the end-users: patients, carers and healthcare professionals.

EBE and EFPIA have performed a detailed analysis of the MDR labelling requirements. From this evaluation, it is considered that justifiable concerns of the legislators in terms of device safe use are already satisfactorily covered by the Medicinal Product Directive (Directive 2001/83/EC). Other device-specific requirements simply appear inapplicable (e.g., UDIs, name of device manufacturer) to prefilled, non-reusable, integral, drug-device combinations.

Labelling requirements for medicinal products

With respect to DDCs, labelling requirements for medicinal products must take precedence over labelling requirements for medical devices.

Since DDCs are regulated as medicinal products, EBE and EFPIA consider that labelling requirements for medicinal products, as specified in Directive 2001/83/EC must, as a general rule take precedence over labelling requirements for medical devices, set out in Annex I of the MDR (“General safety and performance requirements”, and more specifically “Chapter III- Requirements regarding the information supplied with the device”).

Accordingly, the labelling requirements set out in GSPRs are not applicable for DDCs and in principle, are not to be covered by the Notified Body Opinion (NBO).

For example, these requirements include the use of symbols (where possible conforming with international standards). The European Commission’s guideline on *“Readability of the labelling and package leaflet of medicinal products for human use (revision 1, 12 January 2009)”* states that symbols should not replace actual text.



However, the core Instructions for Use (IFU) in the DDC product information particulars (SmPC, package information leaflet; Patient Information Leaflet (PIL) and labels) could be part of the NB review of the device component, based on any Usability ('Human Factors') study data presented that helped develop the proposed IFU.

Instructions for how to administer the drug (with the help of the device component) are typically integrated after Section 6 of the PIL, or sometimes provided as a free-standing 'Instructions for Use' (IFU) document.

Article 59(3) of Directive 2001/83/EC (as amended) provides that the PIL shall reflect the results of **consultations with target patient groups** to ensure that it is legible, clear and easy to use. A European Commission 'readability' guideline specifies that the requirements can be met through user readability testing or with "other methods" (as justified). Handling instructions are part of this and "the use of dummy containers and active demonstration by participants is encouraged." Apart from this, the guideline does not recommend any particular method for user testing.

Concerning the IFU component of the PIL, compliance with applicable requirements of a harmonised norm (e.g. EN 62366) and data from Usability studies whereby the IFU has been utilised, can be used to show conformance with relevant GSPRs. The NBs are qualified and have the expertise to assess such data.

The results of Usability studies conducted by the Applicant, as part of a device Annex I conformance exercise, should be taken into consideration for the demonstration of compliance with the patient consultation requirement in Directive 2001/83/EC (covering the whole PIL).

EBE and EFPIA propose that:

- **it may be beneficial to include the core IFU prepared for the Usability testing (and the study reports) in the Notified Body review**
- **The results of any Usability studies could also form a component of the PIL "readability testing" documentation in the Marketing Authorisation Application (MAA) of the drug-device combination product**
- **the definitive wording in the SmPC and PIL (potentially including a separate IFU) remains within the sole remit of the EMA/NCA, as specified by Directive 2001/83/EC.**

Special considerations

Lastly, EBE and EFPIA highlight two additional considerations where the device labelling requirements in Annex I may need to be incorporated into those requirements beyond that for a medicinal product; (1) innovative DDCs beyond typical medicinal products and (2) use of CMR (carcinogenic, mutagenic or toxic to reproduction) and endocrine-disrupting substances.

- Innovative Drug-Device Combination products beyond typical medicinal products

While the labelling requirements set out by the medicinal product Directive (Directive 2001/83/EC) may be perfectly adequate for well-established categories of DDCs that are typical medicinal products (e.g. syringes), they may be insufficient for more complex and innovative DDCs (e.g. those containing electronics and software).



Respective device standards (such as, but not limited to, e.g. EN IEC 60601-1 “Medical electrical equipment- Part I- General requirements for basic safety and essential performance” as well as EN ISO 11608-1: 2014 “Needle-based injection systems for medical use- Requirements and test methods- Part I: needle-based injection systems”) have specific clauses regarding labelling/Instructions for Use which are important for the safe use of the device. The same is valid for residual risks that are an outcome of the risk management process according to EN ISO 14971 “Medical devices- Application of risk management to medical devices”.

EBE and EFPIA believe the labelling requirements set out in Directive 201/83/EC are adequate for the vast majority of today’s DDCs. However, it is acknowledged that in the future, certain device labelling requirements set out in Annex I of the MDR (Chapter II and Chapter III) could become relevant to complex, innovative, multi-component DDCs (e.g., wearable injectors with cartridges, injectors with wireless controllers or smartphone applications monitoring) on an ‘as applicable’ basis.

- CMR and endocrine-disrupting substances

If CMR and/or endocrine-disrupting substances in the material of the device component exceed 0.1% that may constitute important residual safety risk information under Regulation (EU) 2017/745 (MDR Annex I, Chapter II, Article 10.4.5)

“MDR Annex I; Chapter II; Article 10.4.5: Where devices, parts thereof or materials used therein as referred to in section 10.4.1 contain substances referred to in points(a) or (b) of Section 10.4.1. in a concentration above 0,1% weight by weight(w/v), the presence of those substances should be labelled on the device itself and/or on the packaging for each unit or where appropriate, on the sales packaging, with the list of such substances. If the intended use of such devices includes treatment of children or treatment of pregnant or breastfeeding women or treatment of other patient groups considered particularly vulnerable to such substances and/or materials, information on residual risks for those patient groups and, if applicable, on appropriate precautionary measures should be given in the instructions for use.”

DDCs are regulated under Directive 2001/83/EC, which does not currently have the same labelling requirements.

Therefore, to avoid conflicting interpretations, EBE and EFPIA request that the respective disclosure-, assessment- and labelling requirements for CMR and endocrine-disrupting substances in concentrations exceeding 0.1% by weight of the device component (materials) are clarified with respect to DDCs.

Conclusion

Prefilled, non-reusable, integral, drug-device combinations intended to administer a medicinal product (here referred to as DDCs) are regulated as medicinal products (Directive 2001/83/EC). However, the device component needs to conform with “relevant” General Safety and Performance Requirements set out in Annex I of the Medical Device Regulation (MDR, Regulation (EU) 2017/745).

Annex I of the new MDR contains extensive labelling requirements for medical devices. In the absence of an explicit confirmation that labelling requirements for medicinal products take precedence, there is an obvious risk for different interpretations between Sponsors, Health Authorities and Notified Bodies (NBs).



As a matter of principle, the view of EBE and EFPIA is that the labelling requirements for medicinal products shall take precedence over labelling requirements for medical devices, for this particular category of products.

As an exception, this paper suggests that the "Instructions for Use" for the device component could be within the scope of the Notified Body assessment and Opinion.

In addition, EBE and EFPIA recommend special considerations be given to complex innovative DDCs, use of international symbols and CMR (carcinogenic, mutagenic or toxic to reproduction) and endocrine-disrupting substances.

The labelling recommendations made in this paper should be taken into consideration as guidances and implementing acts are being drafted.



List of abbreviations and definitions

CMR	Carcinogenic, mutagenic or toxic for reproduction substance
EBE	European Biopharmaceutical Enterprises
EC	European Commission
EMA	European Medicines Agency
GSPRs	General Safety and Performance Requirements
IFU	Instructions for Use
Integral DDCs	Integral drug-device combinations. Article 10 in Chapter 1 Scope and definition of the MDR gives the definition of a single integral product: “if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable
MDR	Medical Devices Regulation (Regulation (EU) 2017/745)
NB	Notified Body
NBO	Notified Body Opinion
NCAs	National Competent Authorities
PIL	Patient Information Leaflet
PFS	Prefilled syringe
SmPC	Summary of Product Characteristics
UDI	Unique Device Identification



Annex: Legal and regulatory references

- Article 1(8) of the Medical Device Regulation (Regulation (EU) 2017/745) amends Annex I to Directive 2001/83/EC for medicinal products:

“Any device which, when placed on the market or put into service, incorporates, as an integral part, a substance which, if used separately, would be considered to be a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC, including a medicinal product derived from human blood or human plasma as defined in point 10 of Article 1 of that Directive, and that has an action ancillary to that of the device, shall be assessed and authorised in accordance with this Regulation. However, if the action of that substance is principal and not ancillary to that of the device, the integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004 of the European Parliament and of the Council (1), as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part are concerned”

- Article 1(9) of the Medical Device Regulation (Regulation (EU) 2017/745) amends Annex I to Directive 2001/83/EC for medicinal products:

“Any device which is intended to administer a medicinal product as defined in point 2 of Article 1 of Directive 2001/83/EC shall be governed by this Regulation, without prejudice to the provisions of that Directive and of Regulation (EC) No 726/2004 with regard to the medicinal product. However, if the device intended to administer a medicinal product and the medicinal product are placed on the market in such a way that they form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single integral product shall be governed by Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable. In that case, the relevant general safety and performance requirements set out in Annex I to this Regulation shall apply as far as the safety and performance of the device part of the single integral product are concerned.”

- Article 117 of the Medical Device Regulation (Regulation (EU) 2017/745), amendment to Directive 2001/83/EC for medicinal products:

“Where, in accordance with the second subparagraph of Article 1(8) or the second subparagraph of Article 1(9) of Regulation (EU) 2017/745 of the European Parliament and of the Council, a product is governed by this Directive, the marketing authorisation dossier shall include, where available, the results of the assessment of the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation contained in the manufacturer's EU declaration of conformity or the relevant certificate issued by a notified body allowing the manufacturer to affix a CE marking to the medical device.

If the dossier does not include the results of the conformity assessment referred to in the first subparagraph and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required in accordance with Regulation (EU) 2017/745, the authority shall require the applicant to provide an opinion on the conformity of the device part with the relevant general safety and performance requirements set out in Annex I to that Regulation



issued by a notified body designated in accordance with that Regulation for the type of device in question.”

- Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use
- Labelling requirements for medical devices described within the ‘General Safety and Performance Requirements’ in Annex I (Chapter II, Sections 10.4.5 and Chapter III, Section 23)
- Labelling requirement for medicinal products are described in Directive 2001/83/EC in Article 11, under Title V (Labelling and package leaflet), Articles 54-69 and in Annex I, 1.3 (Summary of product characteristics, labelling and package leaflet)
- Sections relevant to device constituents in the SmPC guideline (European Commission – Notice to Applicants- A guideline on Summary of Product Characteristics (SmPC) - September 2009):
 - **Section 4.2. Posology and Method of administration**
The route of administration and concise relevant instruction for correct administration and use should be given here
 - **Section 6.5 Nature and contents of container**
Reference should be made to the immediate container using the European Pharmacopoeia standard term; the material of construction of the immediate container should be stated ('glass vials', 'PVC/Aluminium blisters', 'HDPE bottles'); and any other component of the product should be listed, e.g. needles, swabs, measuring spoons, syringes inhaler devices, desiccant. The graduation on measuring devices should be explained.
- ISO 15223-1:2016 Medical devices -- Symbols to be used with medical device labels, labelling and information to be supplied -- Part 1: General requirements
 - Requirements for symbols used in medical device labelling that convey information on the safe and effective use of medical devices.
- European Commission Guideline on the readability of the labelling and package leaflet of medicinal products for human use (revision 1, 12 January 2009)
- QRD product information template (version 10.1, June 2019))

