

EBE-EFPIA Position Paper

An Industry Perspective on Article 117 of the EU Medical Device Regulation: Clinical Requirements for Prefilled, Single-Use, Integral Drug-Device Combination Products

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Executive summary

Prefilled, single-use, integral drug-device combinations (DDCs) are regulated as medicinal products. 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 single-use, integral drug-device combination products, the clinical requirements for medicinal products take precedence over clinical evaluation requirements for medical devices. As a pragmatic approach, a Notified Body review of relevant device clinical information would be in the scope of the assessment by the Notified Body for the delivery of the Notified Body’s opinion.

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

Prefilled, single use, integral, drug-device combinations intended to administer a medicinal product (here referred to as DDCs) are regulated as medicinal products (Directive 2001/83/EC).

Paragraph 2 of Article 117 of the Medical Device Regulation (MDR, Regulation (EU) 2017/745) states that such products must comply with relevant *General Safety and Performance Requirements* (GSPRs) set out in the Annex I of the MDR. However, it is noted that whilst GSPRs do not refer to clinical evaluation, it is an expectation of Article 61 of the MDR (as referred to, by Article 5) that conformity with the GSPRs shall be based on clinical data. Whilst it is clear that Article 61 specifically applies to medical devices, it is not clear beyond Annex I, what broader MDR requirements and particularly Article 61 are applicable to the device constituent of an integral, drug-device combination.

In the absence of official guidance on how to interpret Article 117 in this regard, there is an obvious risk that device clinical requirements will come into conflict with clinical requirements for medicinal products. This would create uncertainty both for Sponsors and Notified Bodies (NBs) and lead to divergent interpretations.

EBE and EFPIA have conducted a comparison between medicinal product and medical device clinical requirements as per Directive 2001/83/EC and MEDDEV 2.7/4 “*Guidelines on clinical investigation: a guide for manufacturers and Notified Bodies*”. What transpires is that justifiable concerns of the legislators when developing the MDR in terms of device safe use, are already satisfactorily covered by the medicinal product legislation with regards to clinical utility of the finished product.

Clinical requirements for medicinal products

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

Since DDCs are regulated as medicinal products, EBE and EFPIA consider that medicinal products requirements must take precedence over medical device requirements. That includes the clinical requirements.

A separate device clinical investigation as per Chapter VI “*Clinical evaluation and clinical investigations*” of the MDR is **not** required for medicinal products with an integral medical device, as defined by Article 117 of the MDR.

However, it is acknowledged that a level of clinical information will need to be submitted to support the Notified Body assessment process.

EBE and EFPIA acknowledge that Notified Bodies (NBs) will need to review sufficient evidence to support the safe and effective use of the device, (see Chapter I “*General Requirements*” of MDR Annex I, which likely includes a level of clinical information.



However, the extent of clinical information submitted for Notified Body review should involve a risk-based approach which considers the risk, prior knowledge and prior data on a particular device. For example, a well-established prefilled syringe (PFS) could require less clinical information versus a novel delivery device.

Clinical information content submitted for Notified Body review

While EBE and EFPIA do not advocate for a 'clinical evaluation' approach (as per Chapter VI of MDR and MEDDEV 2.7/1 guideline "*Clinical evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC*"), the following are aspects that are typically incorporated into product development and design control requirements, and as such can be used as supporting evidence to obtain a Notified Body Opinion (NBO):

1. *Scientific literature on the device or equivalent device (precedented use applies)*
 - Peer reviewed publications
 - MAUDE database
2. *Market data*
 - Adverse event (AE) data, customer complaints, recalls, number of sales in EU and ROW, to ensure that data is considered in maintaining patient safety
 - Statistics to compare volume of sales versus device complaint/AE/recalls
3. *Medicinal Product Clinical Trial study/data*
 - Leverage medicinal product clinical trial data involving device

Some companies have previously been requested to collect device information (usability feedback) within medicinal product clinical trials for new novel and/or complex devices. Therefore, it is suggested that, when available, real-life patient handling studies should also be incorporated into this notified body review.

Other considerations

- MEDDEV guideline - 2.7/1 and MEDDEV guideline 2.7/4

It is EBE and EFPIA's position that the clinical evaluation and clinical investigation MEDDEV guidelines (respectively MEDDEV 2.7/1 and MEDDEV 2.7/4) only apply to stand-alone medical devices and do not apply to single use, integral drug device products (DDCs).

- Lifecycle Management

If a substantial change of the device constituent results in a change to the safety, performance and/or intended use of the DDC, clinical evaluation may be impacted and may need reassessment. This should be assessed on a case by case basis. Evidence of clinical benefit should be maintained during the product lifecycle, but it is considered this does not routinely need to be shared with the Notified Body. EBE and EFPIA therefore believe that no requirement for reoccurring assessment relating to clinical evidence from a Notified Body is required, as is the expectation for stand-alone medical devices and maintaining a CE mark. In addition, EBE and EFPIA believe that no continuous post-market surveillance (PMS) role and continual oversight exists for the Notified Body, once a position opinion is granted.



Conclusion

Prefilled, single-use, integral, drug-device combinations intended to administer a medicinal product (here referred to as DDCs) are regulated as medicinal products (Directive 2001/83/EC).

Paragraph 2 of Article 117 of the Medical Device Regulation (MDR, Regulation (EU) 2017/745) states that such products must comply with relevant *General Safety and Performance Requirements* (GSPRs) set out in the Annex I of the MDR. It is noted that according to Article 61 of the MDR, it is expected that conformity with the GSPRs shall be based on clinical data. Whilst it is clear that Article 61 specifically applies to medical devices, it is not clear beyond Annex I, what broader MDR requirements and particularly Article 61 are applicable to the device constituent of an integral, drug-device combination.

In the absence of official guidance on how to interpret Article 117 in this regard, there is an obvious risk that device clinical requirements will come into conflict with clinical requirements for medicinal products. This would create uncertainty both for Sponsors and Notified Bodies (NBs) and lead to divergent interpretations.

It is EBE and EFPIA's views that for single-use, integral drug-device combination products, the clinical requirements for medicinal products shall take precedence over clinical evaluation requirements for medical devices.

However, it is acknowledged that a level of clinical information will need to be submitted to support the Notified Body assessment process.

This paper made recommendations on clinical information to be provided, with the aim that they are taken into consideration as guidance and implementing acts related to integral drug-device combination products get published.



List of abbreviations and definitions

AE	Adverse event
EBE	European Biopharmaceutical Enterprises
EC	European Commission
GSPRs	General Safety and Performance Requirements
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
MEDDEV	European Commission Medical Device Guidance document
MDR	Medical Devices Regulation (Regulation (EU) 2017/745)
NB	Notified Body
NBO	Notified Body Opinion
PMS	Post Marketing Surveillance
PFS	Prefilled syringe
ROW	Rest of the World (i.e. outside EU)



Annex 1: Legal and regulatory references

- 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
- MEDDEV 2.7/1, Rev 4, June 2016, Guidelines on Medical Devices, Clinical Evaluation: A guide for Manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC, European Commission
- MEDDEV 2.7/4, December 2010, Guideline on Medical Devices, Guidelines on Clinical Investigation: A guide for Manufacturers and Notified Bodies, European Commission

