1. Introduction

The subject of this procedure description is the opinion required by a notified body for medicinal products with a medical device component in accordance with Article 117 of Regulation (EU) 2017/745.

2. Background

In Regulation (EU) 2017/745 on medical devices (hereinafter referred to as "MDR"), the scope was extended with regard to so-called integral combination products, i.e. medicinal products with a medical device component. Article 117 amended Directive 2001/83/EC on the Community code relating to medicinal products for human use and, for certain combination products, proof of conformity of the medical device part must be provided in accordance with the general safety and performance requirements (GSPR) in Annex I of the MDR. The manufacturer must submit this evidence to the competent medicinal product authority in its application for marketing authorization. Either a declaration of conformity issued by the manufacturer (sufficient in the event that the involvement of the notified body is not required) or a relevant certificate issued by a notified body, which contains the results of the assessment of the conformity of the medical device part with the GSPR in accordance with Annex I of the aforementioned regulation and which allows the manufacturer to affix the CE marking to the medical device, serves as proof. In the event that both documents are not available, the manufacturer may alternatively submit a Notified Body Opinion with the application for market authorization, which contains the result of an assessment of the conformity of the medical device part with the GSPR of Annex I of the MDR.

3. Impartiality

The principle of impartiality, to which mdc fully commits itself, is a fundamental requirement to be met by the assessments, evaluations, tests and certifications to be performed by mdc. The independence of the personnel is verified both when hiring employees and when selecting and commissioning external auditors, technical experts or testing facilities. A mechanism for ascertaining impartiality has been established. Processes for avoiding and handling conflicts of interest are in place.

4. What are medicinal products with a medical device component that require an opinion in accordance with Article 117 of the MDR?

Products that combine a medicinal product (or an active pharmaceutical ingredient) and a medical device are regulated either by Regulation (EU) 2017/745 on medical devices or Directive 2001/83/EC on medicinal products for human use. The classification of the products according to Article 1(8) second section and 1(9) second section of the MDR is decisive for deciding which regulatory requirements apply.

Integral combination products" ("integral drug device combinations", iCCD for short), which fall under Directive 2001/83/EC, are referred to,

(1) if the main effect of the overall product is attributed to the medicinal product and the medicinal product and medical device are associated with each other at the time of placing on the market
(2) if the medical device is intended to administer the medicinal product and the medical device component is intended to be used exclusively in this medicinal product/medical device combination and is not reusable.

Examples of this type of combination product include autoinjectors, inhalers, prefilled nebulizers, prefilled injectors, prefilled syringes and transdermal patches, insulin injection pens, metered dose inhalers, and co-packaged prefilled syringe with solvent (e.g., water for injection) used to administer the reconstituted drug.

For these combination products, the requirements have been extended by Article 117 of the MDR as of May 26, 2021, and compliance of the medical device part with the GSPR of Annex I of the MDR is now required.

5. Description of the process phases

5.1. Opinion for a new product

5.1.1 Offer and application

The procedure is based on the information that the medical device certification GmbH (hereafter abbreviated to mdc) receives via the questionnaire for the preparation of the offer with the complete necessary information on the applicant organization.
Based on the complete information provided, the interested party will receive a written offer for an opinion in accordance with MDR Article 117. The scope of the assessment is specified by the client in the offer and a flat-rate application fee is charged.
A personal preliminary discussion or telephone information serves to explain the procedure and the requirements. This does not replace self-information about relevant regulations, appropriate training and/or any necessary consultation.
If the offer is accepted by the interested party (from now on: client), the latter sends back the corresponding application with a legally valid signature. Upon receipt of the countersigned application, mdc checks it. Once countersigned by mdc, the application is deemed to be a contract between the two parties. The client receives a written order confirmation with which the documents required for the assessment are requested. In addition, the client will be informed of the assessment team in the form of personnel profiles in good time before the documents are assessed. A team usually consists of one or more persons who have acquired the necessary qualifications and expertise to assess the documents. If the persons are not directly employed by mdc, the client must confirm their agreement or rejection of the proposed persons in writing within two weeks. In the event of rejection by the client, clarification will be sought between mdc and the client and, if necessary, the assessment team will be changed.
If the client agrees, the assessment team will be commissioned by mdc.

5.1.2 Review phase

The assessment and evaluation of the submitted documentation regarding the conformity of the medical device part of the integral combination product with the relevant GSPR of Annex I of the MDR is based on the information submitted by the client. The documentation must be submitted by the client within 6 months of signing the application.
The following documents must be available in German or English:

- Product description
- Intended use of the combination product
- GSPR checklist (including the manufacturer's assessment of the applicability or non-applicability of the respective GSPR, including justification)
- Verification documents for compliance with all applicable GSPR (test reports, assessments, etc.)

If complete technical documentation in accordance with Annex II of the MDR is available, it is advisable to submit it.

The documentation of the assessment result is provided in an opinion in accordance with MDR Article 117. Any non-conformities identified must be rectified by the client and the corresponding verification documents submitted for assessment.

If no final opinion has been received within 12 months of signing the application, the procedure can be terminated by mdc.

5.1.3 Reporting phase

If the Notified Body Opinion has been completed positively and the report has been released, the client receives the opinion for submission to the medicinal product authority responsible for the authorization of the medicinal product. In addition to the positive assessment result, this may also contain further

findings or comments, the examination of which is then the responsibility of the competent medicinal product authority.
No certificate is issued by the notified body. The procedure is deemed to be completed when the final opinion is issued.

5.2. Opinion after a change to the product

5.2.1 Under what circumstances is it necessary to reissue or update the opinion?

The requirements arising from Article 117 of the MDR also apply after a marketing authorization has been granted to all marketing authorizations granted, regardless of whether they already comply with Annex I of Directive 2001/83/EC, Section 3.2, point 12, as extended by Article 117, if major changes are made to a device that may significantly affect the safety and/or performance of the device part or the intended purpose of the device.
A distinction is made between the following two situations in which new or updated opinions must be issued and submitted in accordance with MDR Article 117:

(1) Addition or complete replacement of the medical device part or a component thereof
(2) Modifications to the medical device part or a component thereof that may significantly affect the safety and/or performance of the product part or the intended purpose of the product

The following document can be used as an aid for the evaluation of the change: Position paper for the interpretation of device related changes in relation to a Notified Body Opinion as required under Article 117 of Medical Device Regulation (EU) 2017/745.

In the case of a Notified Body Opinion, it is the responsibility of the marketing authorization holder to determine when a new or updated Notified Body Opinion is required.
As with all other changes, it is the responsibility of the marketing authorization holder of the integral combination product to determine whether the change has a potential impact on the supply, quality, safety or performance of the product. If the marketing authorization holder concludes that there is an impact on the supply, quality, safety or performance of the product, the change must be notified in writing by e-mail and a new opinion must be requested in accordance with Article 117.
As a guideline, at least the following changes require a new opinion by the notified body:

(1) Introduction of a new product as part of a product line extension or a new product variant
(2) Introduction of major changes to existing combination products such as changes to the design, addition or complete replacement of an integrated medical device component, changes to performance characteristics, changes to the intended use that have a potential impact on the provision, quality, safety or performance of the product
(3) Changes to the medicinal product or the active substance component that may affect the performance or safety of a medical device part, e.g. the introduction of a new formulation of the finished medicinal product that results in a different viscosity that significantly affects the performance of the product.

This is without prejudice to the specificities of the product concerned and the fact that the final responsibility for the compliance of the product with the GSPR remains the responsibility of the manufacturer.

5.2.2 Review phase

If one or more conditions for reissuing the opinion in accordance with MDR, Article 117 are met, the notified body must be notified.
As part of a newly submitted questionnaire, the following documents should be submitted together with the notification:

(1) Meaningful description of the change and its impact on the medical device part including references to the previous/original opinion of the notified body.
(2) Identification of the applicable GSPR affected by the change.
(3) Verification documents that prove the conformity of the medical device part with the GSPR of Annex I of the MDR

The assessment and evaluation of the submitted documentation with regard to the conformity of the medical device part with the relevant GSPR of Annex I of the MDR is carried out by a qualified assessment team based on the information submitted by the client.
The result of the assessment is documented in a new opinion in accordance with MDR Article 117.

5.2.3 Reporting phase

If a positive opinion and a final report release are available, the client receives a new opinion for submission to the medicinal product authority responsible for the authorization of the medicinal product. In addition to the positive assessment result, the opinion by the notified body may also contain further findings or comments, which are then subject to review by the competent medicinal product authority.
No certificate is issued by the notified body.

6. Further action by the manufacturer

All applications for marketing authorization submitted to the EMA or national regulatory authorities after 26 May 2021 must demonstrate that the medical device part complies with the relevant requirements of Annex I of Regulation (EU) 2017/745.
The EMA and the national regulatory authorities strongly recommend that the opinion of the notified body be submitted at the time of submission of the dossier for the first application for authorization of the medicinal product in order to allow the procedure to run smoothly.
Confirmations of partial compliance of the medical device part with the relevant GSPR of Annex I of the MDR are not accepted by the EMA's Committee for Medicinal Products for Human Use (CHMP) and the national regulatory authorities.

7. Liability

mdc's liability for damages caused by mdc, particularly in connection with infringements of obligations resulting from the contractual relationship or due to impermissible actions, is limited to the three-fold fee for the respective single order in connection with which the damage has arisen. This aforementioned regulation is not applied if a damage is due to fraud or intentional or grossly negligent behaviour on the part of mdc, nor is it applied in the case of such damages as are due to the infringement of obligations or in the case of damages resulting from injury of life, body or health or in the case of damages for which liability is assumed according to the product liability act. mdc has a liability insurance as required by law with a limit of liability of € 5.000.000 for personal injury, property damage and financial loss. mdc assumes no liability for workers provided by the client for support on occasion of the services to be rendered by mdc according to this contract.