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Guideline on quality documentation for medicinal products when used with a medical device

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Official address Domenico Scarlattilaan 6 • 1083 HS Amsterdam • The Netherlands

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Executive summary

This guideline describes the information that should be presented in the Quality part of a marketing authorisation dossier for a medicinal product when it is used with a medical device, or device part, and submitted in accordance with Directive 2001/83/EC and/or Regulation (EC) 726/2004. This guideline focuses on product-specific quality aspects of a medical device, or device part, that may have an impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of a medicinal product.

This guideline applies in the following cases:

- Medicinal products where the medical device and/or device part and the medicinal product form an integral product that is not reusable (hereafter called integral) and where the action of the medicinal product is principal,
- Medicinal products placed on the market by the Marketing Authorisation Holder (MAH), where the medical device is packed together with the medicinal product (hereafter called co-packaged), or
- Medicinal products, where 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 (hereafter called referenced).

1. Introduction

Increasingly, medicinal products are developed for use with a medical device, or device part; this ranges from a simple prefilled syringe to more advanced autoinjectors to medical devices used as sensors embedded in tablets. Given the wide range of medical devices, or device parts, that may be used with a medicinal product and continuous technological developments, the information provided in submissions has been found to be inconsistent and often incomplete. It is therefore appropriate within the scope of this guideline to provide guidance to quality assessors and the applicant/MAH of a medicinal product on the type of information that should be provided in a submission.

This guideline considers three different, yet common, configurations of medicinal products used with medical devices, and describes the information that should be submitted to a Competent Authority (CA) for each of these configurations.

This guideline also takes into consideration the amendment to Annex I, Directive 2001/83/EC (concerning supportive information to be submitted to CAs) introduced by the Medical Devices Regulation ((EU)2017/745, MDR) by way of Article 117 (see Section 5.4 below).

As discussed herein, depending on the configuration and the potential impact on the benefit-risk assessment of the medicinal product, the information that should be submitted will differ.

The term 'device (part)', as used in this guideline, should be understood to refer to a medical device, or parts of a medical device, that are used in an integral or co-packaged configuration.

In this guideline, the following terminology is used for the three configurations:

Integral: a medical device (part) that falls under the second sub-paragraph of Article 1(8) or the second sub-paragraph of Article 1(9) of Regulation (EU) 2017/745, where the action of the medicinal product is principal:

1. Devices that when placed on the market incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product and has an action that is principal and not ancillary to the action of the device (second sub-paragraph of Article 1(8)). Examples include medicinal products with an embedded sensor where the sensor is a medical device and its action is ancillary to the medicinal product.
2. Devices intended to administer a medicinal product, where the device and the medicinal product are placed on the market in such a way that they form a single integral product intended exclusively for use in the given combination and which is not reusable (second sub-paragraph of Article 1(9)). Typically, these devices have measuring or delivery functions. Examples of medical devices currently authorised for use in integral products include:
 - Single-use pre-filled syringes, single-use pre-filled pens and single-use pre-filled injectors (including autoinjectors) used for the delivery of one or more doses of medicine and which are not intended to be re-used or refilled once the initial doses provided are exhausted.
 - Drug-releasing intra-uterine devices and pre-assembled, non-reusable applicators for vaginal tablets.
 - Dry powder inhalers and pressurised metered dose inhalers that are preassembled with the medicinal product and ready for use with single or multiple doses but cannot be refilled when all doses are exhausted.
 - Implants containing medicinal products whose primary purpose is to release the medicinal product.

For the integral configuration outlined above, the relevant General Safety and Performance Requirements (GSPRs, as set out in Annex I of the MDR) apply with respect to the safety and performance of the device (part). Integral products are discussed in Section 5 below.

The guideline is also applicable to the following configurations where a medicinal product and a medical device are not placed on the market as a single integral unit, but the medicinal product is intended for use with a device.

Co-packaged: A medicinal product and a medical device are packed together into a single pack (e.g. carton), which is placed on the market by the MAH, and

Referenced: The product information (SmPC and/or package leaflet) of the medicinal product refers to a specific medical device to be used (e.g. identified by its brand name and/or specific description), and the specified medical device is obtained separately by the user of the medicinal product.

In both co-packaged and referenced configurations, the medical device should comply with the requirements as laid down by the applicable medical device legal framework. Co-packaged and referenced products are discussed in Section 6 below, where the extent of information provided will vary according to the risks associated with the use of the device with the medicinal product.

Some examples of medical devices co-packaged with, or specifically referenced by, authorised medicinal products include:

- Oral administration devices (e.g. spoons, syringes).
- Injection needles.
- Refillable/reusable (e.g. using cartridges) pens and injectors (including autoinjectors).

- Refillable/reusable dry powder inhalers and metered dose inhalers; spacers for inhalation sprays.
- Nebulisers and vaporisers.
- Single use or reusable pumps for medicinal product delivery.

2. Scope

This guideline provides clarification regarding documentation for medicinal products in respect of a marketing authorisation application (MAA) or post-authorisation applications. This guideline considers the requirements, as laid down in Directive 2001/83/EC and/or Regulation (EC) 726/2004, where the action of the medicinal product is principal. This guideline also reflects current quality assessment practices and defines the additional documents/information for the three configurations described in this guideline. It applies to the following medicinal product types: chemical, biological or radiopharmaceutical.

Section 5 of this guideline primarily considers integral products falling within the definition of second subparagraph of Article 1(9) of the MDR. However, it is recognised that products defined by the second subparagraph of Article 1(8) of the MDR will likely become more common-place as technology develops and medicinal products meeting this definition should follow the basic principles defined herein, recognising that elements of this guideline specifically referring to administration aspects may not be applicable.

This guideline is not exhaustive, and the applicant/MAH (hereafter applicant) should consider all other relevant guidelines related to quality aspects of medicinal products.

Medicinal products utilising electromechanical devices (including active implantable devices), electronic add-ons and digital elements of devices are in the scope of the guideline where they are expected to impact, even potentially, the benefit-risk assessment of the medicinal product from a quality perspective; however, in this regard, it is acknowledged that more detailed guidance may be required in future.

Medicinal products intended to be used with a Class I medical device are also in scope, and requirements are dealt with specifically in the relevant sub-sections below.

Advanced Therapy Medicinal Products (ATMPs)

Article 117 does not apply in the case of combined ATMPs as defined under Article 2(1)(d) of Regulation (EC) No 1394/2007.

The information related to the medical device part(s) of combined ATMPs are detailed in ATMP specific guidelines. Where ATMP specific guidelines do not indicate the location of the relevant information in the dossier, the principles in this guideline should be followed.

The content of this guideline should be taken into consideration in the following cases:

- Medical devices that are co-packaged with ATMPs.
- Separately obtained devices which are referenced in the medicinal product's product information because of their potential impact on the quality, safety and/or efficacy of the ATMP.

For ATMPs, the content of the MAA may be adapted, provided that this is justified under a risk-based approach.

For medical devices that are used as a container closure system for ATMPs, the applicant should provide evidence that the relevant GSPRs are met, for example EU Declaration of Conformity, EU certificate issued by a Notified Body (NB) or confirmation from the applicant in the form of summary information. Section 3.2.R may also include, if relevant, cross-reference to studies or additional information provided in 3.2.P sections.

Information on medical devices used during surgical procedures for application, implantation or administration of an ATMP that may have an impact on the efficacy or safety of the ATMP (as per Annex I, Part IV, Section 5.2.1 of Dir2001/83/EC) is expected in the electronic Common Technical Document (eCTD) Module 5.

The following are out of scope of this guideline:

- a) Veterinary products.
- b) *In-vitro* diagnostic devices, including companion diagnostics.
- c) System and procedure packs regulated under Article 22 of the MDR.
- d) General groups of devices where reference is directly made, or inferred, in the product information, (e.g. "using a syringe or "an infusion line", etc...).
- e) Products falling under the first sub-paragraph of MDR Article 1(8).

3. Legal references, Application of Standards and Guidelines

This guideline should be read in conjunction with:

- Directive 2001/83/EC (the Medicinal Products Directive) and Regulation (EC) 726/2004 (as amended),
- Regulation (EU) 2017/745 on Medical Devices amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, and repealing Council Directives 90/385/EEC and 93/42/EEC.

In addition, this guideline is presented without prejudice and should be read in conjunction with all other relevant directives and regulations forming part of the pharmaceutical *acquis*, the European Pharmacopeia and all relevant European Commission, ICH and CHMP guidelines, Q&A documents and other documents as linked to, or published on, the European Medicines Agency (EMA) website.

4. General Considerations

As a general principle for medicinal products falling within the scope of this guideline, the assessment of the suitability of a device (part) for its intended purpose should take into account the relevant quality aspects of the device (part) in the context of its use with the medicinal product. The complexity of the device (part), relevant patient characteristics and user requirements, as well as the clinical setting or use environment, are also important aspects of the assessment process. The medicinal product dossier should include a discussion of the impact of the device (part) on the Quality Target Product Profile (QTPP), Critical Quality Attributes (CQA) and overall control strategy of the medicinal product.

The amended provisions of point 12 of Section 3.2 of Annex I to Directive 2001/83/EC (introduced by Article 117 of the MDR), require applicants for a medicinal product, where a medical device (part) and

the medicinal product form an integral product that falls under the second sub-paragraph Article 1(8) or the second sub-paragraph of Article 1(9) of the MDR, to submit the results of the assessment of the conformity of the device (part) with the relevant GSPRs set out in Annex I to the MDR (i.e. the EU Declaration of Conformity or the relevant EU certificate issued by a Notified Body). If the application dossier does not contain these results and where the conformity assessment of the device (part), if used separately, requires the involvement of a NB, the applicant is required to provide an opinion on the conformity of the device (part) with the relevant GSPRs, issued by a NB (known as Notified Body Opinion or NBOp). It is the responsibility of the applicant to ensure that the NB is appropriately designated for the issuance of such an opinion by reference to the NANDO website.

Refer to Section 5.4 (3.2.R) below for further details of the documentation required to demonstrate conformity of the device with the relevant GSPRs in Annex I, MDR.

The core precept of this guideline is that the CA responsible for the regulation of medicines will evaluate the device (part) specific aspects relevant to the quality safety and efficacy (and hence overall benefit/risk determination) of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs for the device (part).

This guideline does not define the scope of the NB review, but rather clarifies the type and level of information to be provided as part of the medicinal product dossier, in order to minimise duplication of effort for regulatory authorities, notified bodies and applicants.

This guideline clarifies the documentation that should be submitted in relation to the quality of the medicinal product, including the manufacturing and control methods thereof. It is not intended to, and cannot, address the obligations of the manufacturers of the device (part) in accordance with applicable device regulations. Co-packaged and referenced medical devices should be in compliance with the applicable medical device legal framework.

Where requested or required by a CA, samples of the medicinal product to be placed on the market should be provided. For emerging technologies, and to aid assessment, provision of a sample at time of initial submission is strongly encouraged.

4.1. Submission of data, location in the dossier and format

Relevant information on the device (part) should be presented in a clearly structured manner, following the eCTD format (Volume 2B Notice to Applicants Medicinal Products for Human Use – Presentation and Format of the Dossier). In Sections 5 and 6 below, guidance is provided on information that should be included in specific sections of Modules 1 and 3. To avoid repetition, it is acceptable to cross-reference between sections.

For sections of the eCTD that are not specifically discussed in this guideline (e.g. P.5.2), no specific medicinal product-related aspects are foreseen and the information presented should be in line with the guidance given in the Notice to Applicants.

Regarding Module 3, Section 3.2.P should contain information on the product-specific quality aspects related to the device (part) that may have an impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product. Section 3.2.R should include relevant information related to the demonstration of compliance of the device (part) with MDR Annex I (see Section 5.4 for further guidance).

Usability studies are multidisciplinary in nature and the location of these data is discussed in Section 5.4.

4.2. Use of supporting data

On a case-by-case basis, and where pre-existing data on a medical device (part) used with an already approved medicinal product is available in an applicant's product portfolio, this data could be provided as supportive data in a submission. Discussion and comprehensive justification for the use of this supportive data should be included in Module 3.2.P.2.

4.3. Scientific and Regulatory advice

This guidance cannot cover all types of devices (parts) and/or future technological developments that may raise novel questions and/or require complex scientific assessment. Therefore, consideration should be given to seeking scientific and/or regulatory advice within the EU CA (medicines) network early in development, particularly for new and/or emerging technologies (see also Section 9).

5. Integral Medicinal Products

5.1. Module 1, Product Information

The product information of integral medicinal products should follow the requirements of Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable (see [QRD \[Quality Review of Documents\] templates](#)) and should not include any administrative information on the device (part). The SmPC, labelling and package leaflet should not include details of the device (part) manufacturer/authorised representative, CE mark (including NB number), device symbols, Unique Device Identifier (UDI) or references to device market surveillance reporting.

Information of the device (part) which is necessary for the intended use of the integral medicinal product should be included in the relevant sections of the package leaflet and SmPC, as applicable (for details refer to the SmPC guideline & the [QRD annotated template](#)).

5.2. Module 3.2.P, Drug Product

P.1 Description and Composition

Concise information on integral medicinal products, and brief information on any additional medical device (part)/accessories provided and intended for use with the medicinal product, should be submitted, and their identity (e.g. type/version), description and function should be stated.

P.2 Pharmaceutical Development

This section of the dossier should summarise the information relevant to development of the specific medical device (part) integrated into the medicinal product, including the rationale for its selection in the specific sections of 3.2.P.2. A risk assessment summary for the medicinal product, aligned with relevant risk management principles in ICH Q9, should be presented.

P.2.2 Drug Product

The applicant should take into consideration the intended use of the medical device (part) and its functionality, suitability for use within the context of the medicinal product, the therapeutic indication and the relevant target patient population.

The functional aspects of the medical device (part) should be qualified in line with its complexity and should include the rationale for the choice and optimisation of the relevant aspects of design and performance (such as dose-delivery performance and mechanical functionality of the device (part)).

Where required (e.g. due to changes in medical device (part) design during development), summary bridging data (see Section 7) should be provided in this section of the dossier, with cross-references to relevant data in other modules of the eCTD, as appropriate. Data should be provided to demonstrate and justify the equivalence of the overall performance of the medicinal product prototype(s) used during pivotal clinical development with the medicinal product intended for marketing.

P.2.3 Manufacturing Process Development

A concise description of manufacturing process development for the integral medicinal product should be provided in line with relevant guidance; development and manufacturing processes for the medical device (part) are out of scope. The method of sterilisation of the integral medicinal product, and where applicable, the device (part) should be explained and justified.

A clear narrative of the development history as it pertains to the integral medicinal product including a comparison of the manufacturing process of integral medicinal products from pivotal or bridging clinical studies to the commercial integral medicinal product should be presented.

The development of the control strategy for the integral medicinal product manufacturing process should be described.

P.2.4 Container Closure System (CCS)

The following aspects of the development of the container closure system should be considered:

Description and rationale for integral medicinal product

A brief description of the container closure system should be presented, including, for example:

- Rationale for the container/medical device (part) and materials of construction.
- Critical functional parts e.g. dose-setting mechanism.
- Features to enhance user safety for dose delivery (e.g. audible click), sharps injury prevention features, safety/lock-out features to prevent over-dosage, safe disposal information, etc.
- For implantable/transdermal device (part), information on the matrix and reservoir, including mechanism of drug release etc.
- If the device (part) includes a graduation marking, the requirements of the Quality of Medicines, Questions and Answers, on the EMA website should be considered.

Functional Performance

Those factors that may impact the functional performance of the device (part) should be discussed and considered, e.g. posology, method of administration, physiological factors of the patient population, requirements in other EU guidelines, CHMP recommendations, etc.

Functional performance aspects of the integral medicinal product should be limited to those aspects that impact quality, safety and/or efficacy (and hence overall benefit/risk determination) e.g. dose accuracy and precision over the range of (re)use, mechanical functionality and/or other aspects directly relevant

to the intended use of the device (part) as part of the medicinal product. In particular, the ability of the device (part) to deliver/administer the medicinal product in accordance with the posology stated in Section 4.2 of the SmPC in an accurate and reproducible manner should be demonstrated. In this regard, the following should be considered:

- As far as possible, test conditions should simulate the use of the integral medicinal product under relevant (in-use) storage conditions. This need not necessarily include simulation of interaction with the human body.
- Consistency of dosing (demonstrating that the medical device (part) accurately and precisely delivers the intended dose) should be guaranteed from release until the end of the shelf life, and also during the use of the particular integral medicinal product under the conditions recommended in the SmPC (in-use stability testing). Where transportation studies are not presented in P.3.5, justification should be provided.
- The effects of simulated real-world in-use conditions should be discussed, and data provided as appropriate e.g. shaking, priming, dropping test.

For the above, such studies should be conducted using the intended medicinal product. If the intended medicinal product is not used, the approach should be justified. Furthermore, the studies should be conducted on the device (part) variant to be commercialised, unless otherwise justified. As applicable, conformance to relevant standards should be confirmed.

For usability studies, see Section 5.4 (3.2.R), below.

P.2.5 Microbiological Attributes

For sterile products, the integrity of the integral medicinal product throughout use and shelf-life, as it relates to preventing microbial contamination, should be demonstrated.

P.2.6 Compatibility

Compatibility between all materials in contact with the drug product, including any diluents for reconstitution, should be investigated to provide appropriate and supportive information. The following aspects should be considered:

- All materials in contact with the medicinal product during administration/delivery. Unless otherwise justified, interaction studies should be performed, assessing physical and chemical compatibility (e.g. sorption, precipitation of drug substance in solution, stability, extractable and leachables, etc., as appropriate). Studies should demonstrate no impact on the safety, efficacy and quality of the medicinal product.
- If processing aids (e.g. lubricants, glue/adhesive from labels etc.) are used with the medical device (part) and come into direct contact with the drug product, interaction studies should be performed to evaluate their effects on the drug product as well as on the performance of the device (part), unless otherwise justified. For example, silicone oils released from the device (part) can nucleate the formation of proteinaceous particles/aggregates with protein products. Toxicological assessments of processing aids that are in direct contact with the drug product should be performed, as necessary.
- Compatibility should be considered from a chemical and physical stability perspective i.e. under justified worst-case orientation(s), in-use conditions and during simulated transportation studies.

- The suitability of the device (part) for the particular drug product (e.g. considering the rheological properties of the drug product) should be discussed and justified.

P.3 Manufacture

P.3.1 Manufacturers

Names, addresses and responsibilities for the integral medicinal product manufacturer and batch release sites should be stated, including, as appropriate, sites for assembly of the integral medicinal product, packaging, sterilisation, labelling and quality control. Suppliers of the device (part), and the sites responsible for manufacture or commercial sub-assembly of the device (part) alone need not be stated in this section.

P.3.3 Description of manufacturing process and process controls

The description of the manufacturing process of the integral medicinal product should include operations relating to the integration of device (part) and drug product. Critical processes, technologies and/or packaging operations that directly affect product quality should be described in detail.

The following information should be included:

- Appropriate description of any manufacturing operations that are performed by the integral medicinal product manufacturer to prepare the medical device (part) for the final assembly of the integral medicinal product such as subassembly steps, washing, coating, sterilisation, depyrogenation etc.
- Description of the integral medicinal product manufacturer sterilisation methods and conditions, where relevant. Information on sterilisation of medical device (part) should be presented in this section of the dossier or reference given to another appropriate section in line with relevant EMA guidelines.
- When empty, sterile, ready-to-use container closure components are purchased, information should be provided in line with relevant EMA guidelines. The inclusion of an EU certificate issued by a Notified Body or NBOp including review of sterility is sufficient to assure sterility where applicable. This should be presented in 3.2.R.
- A description of the filling steps and the final assembly of the integral medicinal product, as performed by the manufacturer should be detailed together with critical process parameters and in-process controls.
- Applied labels with a functional role should be described and, when applicable and considered critical, acceptable tolerances for label positioning should be defined.

P.3.4 Controls of critical steps and intermediates

Any critical steps should be justified and critical process parameters, process parameters whose impact on quality cannot reasonably be excluded and in-process controls for the manufacture of the integral medicinal product should be stated, with acceptance criteria. Any device-(part) specific intermediates (sub-assemblies) produced during manufacture of the integral medicinal product should be defined, along with relevant specifications, test methods and their validation. Any holding times should be defined and justified.

P.3.5 Process validation and/or evaluation

Process validation for the integral medicinal product manufacturing process should be performed, as appropriate, in line with relevant European guidelines, including the assembly and sterilisation of the device (part) (if applicable) and any filling steps.

Actual transportation or simulated transport studies that encompass chemical (e.g. degradation under different conditions) and physical (e.g. vibration) aspects to demonstrate stability during transportation should be investigated, where relevant.

P.5 Control of drug product

P.5.1 Specification(s)

The specification should include those parameters that have been identified as CQAs of the medicinal product and that are controlled in the integral medicinal product. When appropriate, the specification should include the following:

- Description/appearance.
- Performance and functionality tests relevant to the intended use of the integral medicinal product e.g. delivered dose uniformity (at release and shelf life) or extractable volume.
- Other critical test parameters related to CQAs of the integral medicinal product where earlier controls are not in place, e.g. glide force, needle penetration force, delivery time, exposed needle length after activation of device (part), activation force, lock-out system control to prevent over-dosing, etc.

P.7 Container closure system (CCS)

Where the device (part) is part of the primary container closure system (immediate packaging) as intended for marketing (e.g. staked-in needle) or forms part of the functional secondary packaging (e.g. pen subassemblies enclosing a pre-filled syringe), the following information should be provided:

- A description of the container closure system, including primary packaging and secondary packaging devices.
- Suitable quality control specifications of the device (part). Specifications should reflect the complexity of the device (part), such that equivalence between devices (parts) from different suppliers can be assured. Unless justified, the supplier of device (part) should be defined in this section.
- Detailed specifications (including description, identification and functional tests as relevant) as well as critical dimensions (with drawings and photographs where appropriate) of primary and functional secondary packaging materials should be provided. Test procedures should be presented, as appropriate.
- For device (part) not in direct contact with the drug product, information commensurate with its functionality for the correct use of the integral medicinal product should be provided. The secondary packaging should take into account the intended user population of the integral medicinal product.
- Primary packaging materials of construction should be described and comply with the relevant Ph. Eur. monographs, if applicable, and food contact directives, as appropriate (e.g. evidenced by

declarations of compliance from suppliers). Where a Ph. Eur. monograph is not available, alternative standards may be referenced with justification.

- Where a material of construction does not meet compendial standards and is used for the first time in a medicinal product, a specification should be included and justified with safety data (as appropriate).

P.8 Stability

Stability studies for the integral medicinal product (or variant, where justified) should include the following tests/studies:

- Functionality tests determined as stability-indicating CQAs for the medicinal product (refer to P.2.4).
- In-use stability testing (including relevant functionality tests) performed under the conditions of use as stated in the SmPC, unless otherwise justified.
- Tests for identified stability-indicating CQAs (e.g. microbial quality, sterility, container closure integrity, content/potency and purity) over the shelf-life and in-use period, as appropriate for the integral medicinal product in question. If necessary, appropriate and scientifically justified alternatives for sterility (such as container closure integrity testing) may be used.

5.3. Module 3.2.A.2, Adventitious Agents Safety Evaluation

All materials of human or animal origin used in the manufacturing process of the integral medicinal product should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided.

TSE agents

Where appropriate, a TSE statement confirming compliance of the part(s) of the integral medicinal product with current, relevant European guidance and standards should be provided.

Viral safety

Where applicable, an assessment of the risk to the integral medicinal product with respect to potential viral contamination should be provided. The viral risk assessment should be performed in accordance with the current, relevant European guidance and standards.

For substances from human blood/plasma, compliance with relevant EU directives, Ph. Eur. and EMA guidelines should be verified.

Other adventitious agents

Detailed information regarding other adventitious agents, such as bacteria, mycoplasma and fungi should be provided in relevant sections pertaining to the device (part) within the core dossier, as appropriate.

5.4. Module 3.2.R, Regional Information, Medical Device

In accordance with Article 117 of the MDR, all applications for an integral medicinal product should include evidence of the conformity of the device (part) with the relevant GSPRs set out in Annex I of Regulation (EU) 2017/745. Refer to the EMA Q&A on Implementation of the Medical Devices and In Vitro Diagnostic Medical Devices Regulations ((EU) 2017/745 and (EU) 2017/746) for further details.

Notified Body Opinion (NBOp)

The processes by which a NB derives their opinion are not within the scope of this guideline.

The assessment of the integral medicinal product can be facilitated when the NBOp is presented as a summary technical report. This enables both assessor and applicant to determine how the opinion was derived, minimise duplication and avoid gaps in assessment, and to identify aspects to be considered during the MAA/variation.

Usability studies

A usability study should be provided in the following situations:

1. Where supporting information is not included in the dossier, and the device (part) has not been used in the intended user population before, taking specific limitations due to the indication and/or disease into account, or
2. Where other aspects of the intended use, including changes to the clinical setting or use environment are new or different from the intended use as confirmed by the EU certificate issued by a Notified Body or NBOp.

In these cases, and in the cases where no NBOp is needed, detailed information on use-related risks and results of usability studies (or justification for their absence) should be presented in Module 3.2.R (cross-referencing data in Module 5, if relevant). Usability is considered a multidisciplinary topic and may also be assessed outside of quality considerations.

Where evidence of usability is required, this may be supported by published and/or other relevant data for an identical/equivalent device (part) on the market. In this case, relevant data could be bridging data to an identical/equivalent device (part) used in different patient populations. However, if usability cannot be satisfactorily demonstrated in this way, a formal usability study is required to demonstrate safe and effective use of the integral medicinal product by the intended user population. Applicants are encouraged to follow/use relevant EU harmonised standards to demonstrate compliance.

Use of Supportive Data

Detailed information pertaining to the discussion presented in Section 4.2 above should be presented in this section.

6. Medicinal Products with Co-packaged or Referenced Devices

Where a medical device is co-packaged or referenced in the product information of the medicinal product, additional information on the device may be needed. The extent of the additional information will depend on the specifics of the device, its intended use and the risks thereof to the quality, safety and/or efficacy, and hence overall benefit/risk determination of the medicinal product under consideration (e.g. compatibility, extractables and leachables, etc). There are separate sections for devices that are co-packaged and for those that are referenced.

6.1. Medicinal Products with Co-packaged Devices

This configuration includes products where a co-packaged medical device is intended to be used only for the administration and/or application of the co-packaged medicinal product.

6.1.1. Module 1, Product Information

The product information of a medicinal product including a co-packaged device should follow the requirements of Directive 2001/83/EC or Regulation (EC) No 726/2004, as applicable (see QRD templates) and should not include any administrative information on the medical device. The SmPC, labelling and package leaflet should not include details of the device manufacturer/authorised representative, CE mark (incl. NB number), device symbols, UDI or references to device market surveillance reporting.

Relevant information for the use of the co-packaged device, especially if necessary for the intended use of the medicinal product with the device should be included in the appropriate sections of the medicinal product package leaflet and SmPC, as applicable (for details, refer to the SmPC guideline & the [QRD annotated template](#)).

The MAH of the medicinal product is responsible for the co-packaged medicinal product and its traceability (including the co-packaged device), and hence only the contact details of the MAH should be on the package leaflet/labelling.

The co-packaged device must also be in conformity with the MDR, which includes compliance with labelling requirements specific to the device.

6.1.2. Module 3.2.P, Drug Product

P.1 Description and Composition

A brief description, including function and identity (e.g. type/version) of any device(s) with which the medicinal product will be used or administered and which will be supplied along with the medicinal product should be stated.

P.2 Pharmaceutical Development

This section of the dossier should summarise the information on the proposed medical device relevant to development of the medicinal product, in the appropriate sections of 3.2.P.2. The use of a medicinal product with a specified device should be demonstrated to be safe and effective. The amount of information provided in this section should reflect the risk of the device to impact the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product. In certain cases, the impact of the method of sterilisation of the device (e.g. ethylene oxide) on product quality should be understood.

The information provided in P.2 is not expected to be as detailed as the information provided in 3.2.R for the device (i.e. cross-referencing with relevant sections of 3.2.R is possible).

P.2.2 Drug Product

A general discussion on the choice of device should be provided, including the intended use, rationale for choice of device, etc.

The functional aspects of the device should be qualified in line with its complexity and should include the rationale for the choice and optimisation of the design and performance (such as dose-delivery performance and mechanical functionality of the device). Dose accuracy/delivered dose uniformity should

be demonstrated with the medicinal product. Any markings/graduation should be justified in line with the posology stated in Section 4.2 of the SmPC. Details of the cleaning of the device(s) should be stated in Section 6.6. of the SmPC, where relevant and in the Package Leaflet.

Where changes are made to the device during clinical development, refer to Section 7.

P.2.5 Microbiological Attributes

For medicinal products intended to be used in a sterile manner, the sterility of the device is assumed as long as the device is supplied in its primary packaging with the sterile barrier intact. Maintenance of sterility of the medicinal product throughout its in-use period, and under the conditions of its intended use, should be discussed and justified.

P.2.6 Compatibility

Unless otherwise justified, compatibility between device and drug product should be investigated:

- Compatibility should be considered from an in-use stability perspective and the physical and chemical compatibility of the drug product with the device(s) should be demonstrated (e.g. sorption, precipitation of drug substance in solution, stability, etc.). Interaction studies should be performed, as appropriate, using a risk-based approach. All materials in contact with the drug product should be considered in an appropriate manner and having regard of contact time.
- The suitability of the device for the particular drug product (e.g. considering the rheological properties of the product) should be discussed and justified.

P.7 Container Closure System

The device is not part of the container closure system and thus only a brief description of the device should be provided in this section (for example; “1 mL glass syringe including 0.05 mL marked graduations”, along with the name and/or base-UDI of the device). Where appropriate, a specification, as applied to the incoming device upon receipt by the medicinal product manufacturer, should be presented. For further details, reference should be made to the information in 3.2.R, including evidence of compliance with the applicable medical device legal framework.

Where the co-packaged medical device becomes part of the container closure system prior to administration or application (for example a finished product transfer device attached to a vial) the device should prevent microbial ingress and maintain the sterility of the medicinal product throughout its use.

P.8 Stability

If relevant, in-use stability data should be provided for the drug product in contact with the device, including parameters for device functionality that may impact the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product. The shelf-life of the medicinal product should be set based on the shortest expiry date of all components of the medicinal product and a co-packaged administration or application device(s) marketed as a single unit.

6.1.3. Module 3.2.A.2, Adventitious Safety Evaluation

An EU certificate or EU Declaration of Conformity can be accepted as evidence of compliance of the device (part) with EU requirements.

6.1.4. Module 3.2.R, Regional Information, Medical Device

Evidence should be provided that relevant standards have been met e.g. EU Declaration of Conformity or, where applicable, EU certificate, or other appropriate documentation such as summary information confirming compliance with relevant GSPRs.

Where required and applicable (e.g. owing to changes in device design), summary bridging data should be provided in this section of the dossier, with cross-reference to relevant data in Module 4 or Module 5, as appropriate (see Section 7).

If the device has not been used in the proposed patient population before, or if the setting of use is new, a usability study is expected. Evidence of usability may be supported by published or other relevant data for identical/similar devices on the market. Relevant data could also include bridging data to similar devices or to the same devices used in different patient populations. However, if usability cannot be satisfactorily demonstrated in this way, a formal usability study is required to demonstrate safe and effective use of the medicinal product by the intended user population. Applicants are encouraged to follow/use relevant EU harmonised standards to demonstrate compliance.

A summary should be provided in Module 3.2.R, cross-referring to Module 5, where information on usability studies (or justification for their absence) should be presented.

Discussion of, and justification for the use of supportive data should be included in this section (for further detail, see Section 4.2 above).

6.2. Medicinal Products with Referenced Devices

Where a medical device is referenced in the product information of the medicinal product and may have a potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product, additional information may be required. The requirements in this section do not apply where reference is made to a general group of devices (e.g. "using a syringe" or "an infusion line", etc.).

The impact of the referenced device on the medicinal product when used together should be considered using a risk-based approach, taking into account the need for a usability study. Evidence of safety and/or bioequivalence/efficacy for the medicinal product used with the device should be provided as appropriate.

The product information should be sufficiently detailed to ensure correct use of the medicinal product with the referenced device. Refer to Section 6.1.1 above.

In section 3.2.P.2, data on compatibility, dosing accuracy, functionality, handling, manipulation, etc., should be presented as appropriate.

In section 3.2.P.8, in-use stability data should be presented, if applicable.

Information on usability studies should be presented, unless otherwise justified (see Section 6.1.4 above).

7. Bridging to Devices used in Clinical Development

While authorisation of clinical trials is within the competence of national CAs (and hence outside the remit of this guideline), in the context of a MAA, the following guidance is provided:

- Given the (often) critical contribution that a device makes to the safe and effective administration or application of a medicinal product, the device (part) should be as advanced as possible in the development process (e.g. meets relevant GSPRs) by the time pivotal clinical trials (that include the device (part)) commence. This will subsequently reduce the potential need for extensive bridging data at time of marketing authorisation.
- The impact of any changes in the device during pivotal clinical trials should be described, evaluated and justified in terms of any potential impact on the quality, safety and/or efficacy (and hence overall benefit/risk determination) of the medicinal product as applicable for the particular configuration (e.g. delivered dose, needle penetration force for subcutaneous/intramuscular injection, usability factors). Where changes are made, data to bridge the changes from a quality, safety and/or efficacy perspective may be required. Appropriate data should be provided to demonstrate and justify the equivalence of the overall performance during clinical phases with that at time of MAA.
- Quality-relevant aspects should be discussed in Module 3.2.P.2.2, and should describe the changes, the batches used and trial(s) affected, as well as the mitigation measures applied to ensure that the impact on product quality was minimal.

8. Lifecycle Management

The MAH should ensure that they are aware of any changes made to the device (part) used in an integral or co-packaged medicinal product. Depending on the nature of the change, the MAH should determine whether updates to relevant documentation in the eCTD (e.g. specifications, etc.) are required.

Variations to the dossier related to a device (part) should be submitted in accordance with Commission Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use, and associated variation guidelines.

The category of variation should take into consideration the impact of the change, particularly where a change impacts any medicinal product CQA and/or any element of the overall medicinal product control strategy. In cases where the need for a variation is unclear and/or the category of the change is unclear, it is recommended that the medicines CA that issued the marketing authorisation be consulted to agree the category prior to submission of the variation application.

The MAH should also consider whether changes to the medicinal product (e.g. changes to volume, viscosity, etc.) may impact the performance of the device (part), in such a way that its use may require further verification and/or validation. In addition, changes in the intended use or target population may require an additional usability study.

Additional considerations

In cases where a variation application is submitted to change, replace or add a device (part) or other aspect of the user interface, consideration should be given to whether there is an impact on the product information that may affect the potential risk of medication errors. The overall risk assessment of the medicinal product should be updated accordingly, with consideration given to the following:

- The need for communication with patients and/or health care professionals regarding the change.
- Where differences exist, the risks of potential medication errors should be assessed. Additional usability studies may be required, as determined by the outcome of this risk assessment.
- If there is a risk of a medication error because of the change, this may need to be captured in the Risk Management Plan (RMP).

9. Emerging Technologies

It is recognised that there are rapid developments in science and technology for both medical device (part) and medicinal products. Whilst this guideline discusses information that should be provided in an MAA or post-authorisation application, alternative approaches for emerging technologies may be acceptable, where adequately justified.

For a medicinal product utilising emerging technologies, it is recommended to engage with the relevant medicines CAs in a timely manner, e.g. by requesting formal scientific advice, or through an Innovation Office, etc. It is also recommended to identify a NB and engage in discussions in a timely manner.

10. Definitions

Applicant

The commercial entity responsible for the marketing authorisation application or post-approval application in the EU.

ATMP

Advanced Therapy Medicinal Products (ATMPs, as per Regulation 2007/1394 EC) are medicines for human use that are based on genes, tissues or cells.

Control Strategy

A planned set of controls derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance, drug product, medical device (part), facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control.

Container Closure System (CCS)

The sum of parts that together contain and/or protect the drug product. This includes immediate and secondary packaging, where the latter is intended to provide additional protection to the drug product. The container closure system may include medical devices (or device parts), as defined in Section 1 of this guideline.

Device (synonym: Medical Device)

A device that fulfils the definition of a medical device, as defined in the relevant EU legal framework, and is intended to be placed on the EU market or made available on the EU market. This also applies to part of a device that fulfils the definition of Article 2(1) MDR.

Dossier

The complete body of data submitted for regulatory assessment. In this case, the dossier refers to the administrative and quality constituents of the eCTD, i.e. Module 1 (administrative), Module 2 (Overall Summaries) and Module 3 (quality) respectively, and (typically) more specifically to the content of Module 3.

Marketing Authorisation Holder (MAH)

The company that has been granted a marketing authorisation for a medicinal product by a competent authority of a member state in accordance with Directive 2001/83/EC (as amended) or by the European Commission in accordance with Regulation (EC) No 726/2004, and is responsible for marketing the medicinal product.

Medical Device Manufacturer

The commercial entity manufacturing and supplying sterile/non-sterile devices and/or device parts to the medicinal product manufacturer.

Medicinal Product Manufacturer

The physical location and commercial entity legally responsible for the manufacture of the integral and/or co-packaged medicinal product.

Notified Body Opinion (NBOp)

An opinion provided by a Notified Body on the conformity of a device (part) with the relevant GSPRs set out in Annex I of Regulation 2017/745, as required by Article 117 of the MDR.

Usability

The level to which a medicinal product can be handled in accordance with the product information in the different settings where it may be used, taking into account the variety of patient characteristics, the risk for medication errors and the impact to the patient and caregiver's quality of life, etc. Therefore, this definition includes (and is not limited) to that presented in IEC 62366.

Abbreviations

ATMP	Advanced Therapy Medicinal Product
CA	Competent Authority (for the regulation of medicines, either National or EMA)
CCS	Container Closure System
CHMP	Committee for Human Medicinal Products
CQA	Critical Quality Attribute
eCTD	electronic Common Technical Document
EMA	European Medicines Agency
GSPR	General Safety and Performance Requirement
ICH	International Council for Harmonisation of Technical requirements for Pharmaceuticals for Human Use
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR	Medical Device Regulation (EC 2017/745)
NB	Notified Body
NBOp	Notified Body Opinion
Q&A	Questions and Answers
QRD	Quality Review of Documents group, EMA
QTTP	Quality Target Product Profile
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy
UDI	Unique Device Identifier