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Guideline on the quality requirements for drug-device combinations

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Executive summary

This guideline provides guidance on the documentation expected for Drug-Device Combinations (DDCs) in the quality part of the dossier for a marketing authorisation application or a variation application.

For the purpose of this guideline, medicinal products which contain one or more medical devices(s) as an integral part of the composition, as well as medicinal products for which one or more medical device(s) and/or device component(s) are necessary for use of the medicinal product are defined as DDCs. The types of DDCs within the scope of this guideline are medical device(s) and/or device component(s) that are integral to the medicinal product or non-integral (i.e. co-packaged with the medicinal product or referenced in the medicinal product information and obtained separately).

1. Introduction (background)

In recent years there has been an increase in the number of scientific advice requests and marketing authorisation applications (MAAs) where a medicinal product incorporates, either in an integral or non-integral manner, a medical device/medical device component (hereafter, both terms are called "device(s)", for definitions see Section 10) for the use of the medicine.

The availability of commercialised devices with automated functions is increasing and this may benefit patients with regular and long-term dosing requirements in an outpatient setting, either by self-administration or with the support of a professional or lay caregiver. This reduces the burden on patients and on healthcare systems.

In this guideline, the terms 'integral' and 'non-integral' are used to describe DDCs as follows:

Integral DDCs are products falling under the second sub-paragraphs of both Article 1(8) and Article 1(9) of the Regulation (EU) 2017/745 on medical devices (the MDR). These Articles describe the two types of integral drug-device combination products authorised under the medicines' framework:

1. Devices that when placed on the market or put into service incorporate, as an integral part, a substance that, if used separately, would be considered as a medicinal product, provided that the action of the substance is principal (Article 1(8) MDR).
2. Devices intended to administer a medicinal product, where they form a single integral product intended exclusively for use in the given combination and which is not reusable (Article 1(9) MDR). Typically, these devices have measuring, metering or delivery functions.

Examples of medical devices in integral DDCs are:

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

- Implants containing medicinal products whose primary purpose is to release the medicinal product.
- Medicinal products with an embedded sensor.

Non-integral DDCs are those DDCs for which the two or more separate components (i.e. medicinal product(s) and device(s)) are not physically integrated during manufacturing but where the medicinal product and the specific device(s) are combined for administration.

Devices in non-integral DDCs are those that are co-packaged and supplied along with the medicinal product, or where the Product Information (SmPC and Package Leaflet) refers to a specific device to be used with the medicinal product but the device is obtained separately. In either case, devices not falling within the scope of Article 1(8) and 1(9) of the MDR should be CE marked. Non-integral medical devices that are co-packaged and those that are obtained separately are discussed in separate sections of Chapter 6.

Examples of medical devices in non-integral DDCs are:

- Oral administration devices (e.g. cups, spoons, syringes)
- Injection needles and filter needles
- Refillable pens and injectors (e.g. using cartridges)
- Reusable dry powder inhalers; spacers for inhalation sprays
- Nebulisers, vaporisers
- Pumps for medicinal product delivery
- Electronic tablet dispensers

2. Scope

DDCs falling within the definition of Article 1(9) of the MDR are the primary focus of this guideline; however, it is recognised that DDCs as defined by Article 1(8) of the MDR will likely become more common-place as technology develops. DDCs falling within the definition of Article 1(8) of the MDR are within the scope of this guideline and should follow the basic principles defined herein, recognising that certain elements of this guideline may not be applicable. It is also recognised that not all aspects of this guideline may be applicable depending on the type of DDC. In such cases, it is recommended to consult with a competent authority for the regulation of medicines or seek scientific advice. This guideline is not exhaustive, and applicants should also consider all other relevant guidelines related to quality aspects of medicinal products.

This guideline covers specific quality dossier requirements to be provided for in an MAA and subsequently during the product lifecycle for integral and non-integral DDCs, as defined in the introduction. It applies to DDCs where the medicinal product constituent is either a chemical, biological or radiopharmaceutical.

With respect to ATMPs, this guideline applies only to devices that are considered part of the container closure system, or medical devices that are co-packaged or referenced in the Product Information and obtained separately. Article 117 of the MDR does not apply to ATMPs.

The following are out of scope of this guideline:

a) Combined ATMPs (where devices are part of the active substance and/or the formulation). The ATMP Regulation 1394/2007 applies for MAAs for combined ATMPs.

b) Electromechanical components of devices (including active implantable devices) and electronic add-ons to existing products.

c) Veterinary DDCs.

d) *In-vitro* diagnostic devices.

e) Medical devices incorporating, as an integral part, a medicinal substance or human blood derivative with a mode of action ancillary to that of the device.

3. Legal basis

This guideline should be read in conjunction with:

- Directive 2001/83/EC (the Medicinal Products Directive, MPD) and Regulation 726/2004/EC (as amended), and
- Regulation (EU) 2017/745 on medical devices (the Medical Devices Regulation, MDR) which amends Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009, and which repeals Directive 93/42/EEC (the Medical Device Directive, MDD).

In addition, this guideline should be read in conjunction with all other relevant directives and regulations, the European Pharmacopeia and all relevant Commission, ICH and CHMP guidelines, Q&A documents and other documents as linked to or published on the EMA website.

4. General considerations

As a general principle for the DDCs considered in this guideline, the assessment of the suitability of a device for its intended purpose should take into account both the relevant quality aspects of the device itself and its use with the particular medicinal product. The complexity of the device, relevant patient characteristics and the clinical setting in which the DDC is to be used are also important aspects of the review process. The medicinal product dossier should include full evaluation of the impact of the device on the Quality Target Product Profile (QTTP), Critical Quality Attributes (CQA) and overall control strategy of the medicinal product.

In accordance with Article 117 of the MDR, an MAA for an integral DDC shall include evidence of the conformity of the device part with the relevant General Safety and Performance Requirements (GSPRs) as follows:

1. Where available, an EU Declaration of Conformity issued by the device manufacturer, or a Certificate of Conformity issued by a Notified Body (NB) that allows a CE mark to be displayed on the device.

2. If the above information (on results of the conformity assessment) is not available:

   (a) for medical devices that, if used separately, do not require the involvement of a NB, the applicant's confirmation that the device part meets the relevant GSPRs, or

   (b) if the conformity assessment of the device, if used separately, would require the involvement of a NB, a Notified Body opinion (NBOp) on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB.

Refer to Section 5.4 (3.2.R) below for further details.

The **core precept** of this guideline is that the Competent Authority for the regulation of medicines (CA) will evaluate the device specific aspects of safety and performance relevant to the quality, safety and efficacy of the medicinal product, and that, as applicable, the NB will assess the relevant GSPRs.

Non-integral DDCs should be CE marked in accordance with the MDR. Where a CE marked device for the administration of the medicinal product is co-packaged or is referred to in the SmPC of a marketing authorisation, additional information may need to be provided by the applicant with regards to the device if the device may have an impact on the quality, safety and/or efficacy of the medicinal product.

In cases of doubt as to the proposed classification of the device according to the MDR, it is recommended that an opinion be sought from a medical device CA.

The requirements laid down in the guideline relate to the quality of the DDC, including the manufacturing and control methods thereof. It is not intended to address the obligations of the manufacturers of the medical device(s). It is however, acknowledged that specific information may be required to fulfil the requirements of other EU guidance (e.g. ICH guideline M7).

Samples of the DDC should be provided on request.

4.1. Application of Standards

Compliance of a DDC with relevant Ph. Eur. chapter(s) or monograph(s) should be demonstrated. Ph.Eur. requirements and European and ICH guidance take precedence over ISO standards.

4.2. Submission of data, its location in the dossier and its format

Information on the device should be provided in a clearly structured manner, following the electronic Common Technical Document (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 to be included in specific sections of Modules 1-3. Cross-reference may be made between sections in order to avoid repetition.

With regards to the structure of Module 3, Section 3.2.P should contain information on the product-specific quality aspects related to the device relevant to the quality, safety and efficacy of the medicinal product. Section 3.2.R should include relevant information related to the demonstration of compliance of the device(s) with MDR Annex 1 (the GSPRs) e.g. NBOp, NB Certificate of Conformity and/or device manufacturer's EU Declaration of Conformity.

In general, Module 3 of the MAA dossier should include appropriate information on the manufacture, control and usability of the DDC as defined for the intended patient population. Usability and human factor studies are multidisciplinary in nature and could be included in section 5.3.5.4, 'Other Clinical Study Reports' of the CTD, with appropriate reference to Module 3 as these may be reviewed by both pharmaceutical and clinical assessors, each with different focus.

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

4.3. Platform technology/technologies

Discussion and justification for the use of platform technology/technologies (for definition, see Section 10) should be included. A summary of the (relevant) data for those aspects of the device which pertain

to the 'platform' should be presented; these should be clearly indicated in relevant sections of Module 3.2.P and should include references to detailed information presented in 3.2.R. Suitability with regards to specific products and subsets of the target patient population should be demonstrated. Reference to previously approved DDC(s) developed and marketed by the marketing authorisation holder (MAH) may be included as supportive information, as well as other relevant quality aspects in support of the proposed approach.

4.4. Scientific advice

This guidance covers the main aspects of the quality requirements for DDCs to be submitted as part of an MAA. However, it is not possible to cover all types of devices and/or future technological developments that may raise novel questions and/or require complex scientific assessment. Consideration should be given to seeking advice within the EU Competent Authority (medicines) network early in development, particularly for new and/or emerging technologies (see Section 9).

5. Integral DDCs

5.1. Module 1, Product Information

SmPC Section 1: The name of the medicinal product should include the device presentation in line with EDQM standard terminology for pharmaceutical form.

SmPC Section 4.2: The directions for proper use of the DDC should be described (including cleaning of the device as necessary), in line with relevant guidance. A device tradename may be stated.

SmPC Section 6.3: Information on DDC in-use shelf-life should be included, if relevant.

SmPC Section 6.4: DDC storage conditions should be listed.

SmPC Section 6.5: The type of the device(s) and its (their) component material(s) should be listed.

SmPC Section 6.6: Product-specific information should be provided for preparation or handling (including disposal of the device(s)).

Package Leaflet: Information should be consistent with the SmPC, provide clear and simple instructions on the intended use of the DDC for patients and/or for healthcare professionals (HCP) and be written in such a way as to prevent medication errors. Information related to the use of the DDC, consistent with the device Instructions For Use (IFU), if applicable, should be included.

Package leaflet and labels: The outer packaging and the Package Leaflet may only include symbols or pictograms if necessary, to clarify certain information compatible with the SmPC (e.g. instructions for use) which may be useful for the patient, to the exclusion of any element of a promotional nature.

For a device that has a CE mark, the CE mark may be included on the device itself but should not be included on the labelling for the DDC as this may be interpreted incorrectly as referring to the DDC as a whole.

5.2. Module 3.2.P, Drug Product

P.1 Description and Composition

Concise information on integral DDCs, and if applicable, any additional devices provided and used with the medicinal product, should be submitted. The description and function of each device should be stated.

P.2 Pharmaceutical Development

This section of the dossier should summarise all information relevant to development of the device as integrated into the medicinal product, including the rationale for its selection. The suitability of the device for its intended use, in the context of the device performing as intended and protecting the medicinal product etc., should be demonstrated. A clear narrative of device and medicinal product development including all relevant data (e.g. justification of any new device, pharmaceutical form, etc.) should be provided. The suitability of the DDC and its materials of construction to protect the drug product formulation from light, moisture, microbial contamination and vapour phase permeation (as appropriate) should be confirmed. Any interactions of the device with the medicinal product should be discussed and justified, as appropriate.

It is recommended that a risk assessment summary for the DDC, aligned with suitable risk assessment principles in ICH Q9 and/or DIN EN ISO 14971, is presented.

P.2.1 Components of the Drug Product

A high-level description of the DDC should be provided, cross-referring to other sections as appropriate.

P.2.2 Drug Product

The applicant must take into consideration the intended use of the device and its suitability within the context of the DDC, its therapeutic indication and the relevant target patient population.

Where required (e.g. due to changes in device 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 Module 4 or Module 5, as appropriate. Appropriate data should be provided to demonstrate and justify the equivalence of the overall performance of the DDC prototype(s) used during pivotal clinical development with the DDC intended for marketing.

P.2.3 Manufacturing Process Development

A concise description of the DDC manufacturing process development should be described in line with relevant guidance. The development, justification and suitability of sterilisation processes of any devices or the DDC should be described, where relevant.

A comparison of the manufacturing process of DDCs from pivotal or bridging clinical studies to the commercial DDC should be presented.

The development of the control strategy for the DDC 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 DDC

A brief description of the container closure system should be presented, including the rationale for the container and device component(s) and its (their) materials of construction, including, for example:

- Any non-integral medical devices needed for correct use of the DDC.
- Confirmatory signals 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 devices, information on the matrix and reservoir, including mechanism of drug release.
- Brief details of critical functional components e.g. power supply, dose-setting mechanism, description of controls and alarms and their instructions for use etc.
- Brief description and rationale for any related technologies e.g. a software application.
- If the device includes a graduation marking, the requirements of Quality of Medicines, Questions and Answers on the EMA website should be considered.

Functional Performance

Functional performance aspects of the DDC should include dose accuracy and precision, mechanical functionality and/or other functionalities directly related to the intended use of the device with the medicinal product and its impact on quality, safety and/or efficacy.

The ability of the device to deliver the medicinal product in an accurate and reproducible way should be demonstrated as per the posology stated in Section 4.2 of the SmPC. The following should be considered:

- Test conditions should, as far as possible, simulate the use of the DDC (e.g. dose delivery performance from an eye drop bottle should be evaluated from the dropper in various orientations) under relevant (in-use) storage conditions.
- Consistency of dose delivery should be demonstrated throughout the (in-use) shelf-life of the DDC (e.g. beginning, middle and end). The precision and accuracy of dosing should be guaranteed from release until the end of shelf life and also during the use of the particular DDC under the conditions recommended in the SmPC (in-use stability testing).
- Issues related to usage e.g. shaking, priming, dropping test.

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

Compatibility

Compatibility between device and drug product should be investigated to provide appropriate and supportive information. The following aspects should be considered:

- The physical and chemical compatibility of the drug product with the device(s) should be demonstrated. All materials in contact with the drug product should be considered. Interaction studies, including extractable and leachable studies as appropriate, should be performed. These

should include physical and chemical compatibility (e.g. sorption, precipitation of drug substance in solution, and stability, etc.).

- If processing aids (e.g. lubricants, glue/adhesive from labels etc.) are used with the device and come into direct contact with the drug product, leachable studies should be performed to evaluate their effects on the drug product as well as on the performance of the device(s). For example, silicone oils released from the device components 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 different orientations, in-use conditions and during simulated transportation studies.
- The suitability of the device for the particular drug product (e.g. considering the rheological properties of the drug product) should be discussed and justified.

P.2.5 Microbiological Attributes

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

P.3 Manufacture

P.3.1 Manufacturers

Manufacturer names/addresses for DDC assembly, packaging, DDC sterilisation, labelling and quality control sites, as well as for the EU batch release site(s) should be stated.

P.3.3 Description of manufacturing process and process controls

The description of the manufacturing process of the DDC should include operations relating to the combination of device(s) 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:

- Description of any operations that are performed on the device(s) by the DDC manufacturer (such as subassembly steps, washing, coating, sterilisation, or depyrogenation etc.). Information on the sites performing these steps could be presented in this section of the dossier or reference given to section P.7.
- Description of the DDC manufacturer(s)' sterilisation methods and conditions for the device(s), where relevant. The sterilisation method(s) used should be validated.
- A description of the filling steps and the final assembly of the device(s) into the DDC, as performed by the DDC manufacturer should be detailed together with critical process parameters, in-process controls and acceptance criteria (for critical steps).
- For applied labels which include printed markings, the position of the label on the container should be specified and acceptable tolerances for the label positioning defined as critical in-process controls (IPCs) in Module 3.2.P.3.3 and Module 3.2.P.3.4.

P.3.4 Controls of critical steps and intermediates

Any critical steps should be justified, and any device-specific intermediates 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 manufacture of the DDC should be performed in line with relevant European guidelines, including the assembly and sterilisation of the device(s) (if applicable) and any filling steps.

P.5 Control of drug product

P.5.1 Specification(s)

When appropriate, the specification should include the following:

- Description of DDC appearance.
- Performance tests relevant to the intended use of the DDC e.g. extractable volume, delivered dose uniformity and functionality of the device at both release and shelf life.
- Other critical test parameters related to CQAs of the medicinal product, e.g. glide force, needle penetration force, seal integrity, delivery time, exposed needle length after activation of device (needle penetration depth, relevant to route of administration), activation force, transdermal adhesion properties, lock-out system control to prevent over-dosing and signals to confirm dose delivery to the patient/user.

P.7 Container closure system

Where the device is part of the container closure system as intended for marketing, the following information should be provided:

- A description of the container closure system, including the materials of construction of each primary packaging and device component and its specification.
- Information on sites and processes for sterilisation and/or subassembly of device(s), or reference to section P.3. When empty, sterile, ready-to-use container closure components are purchased, information should be provided in line with the EMA Sterilisation guideline (EMA/CHMP/CVMP/QWP/BWP/850374/2015). Where a sterile CE-marked device is used, the inclusion of the NB Certificate of Conformity is sufficient to demonstrate sterility.
- Suitable quality control specifications of medical device(s) and/or device components.
- Detailed specifications and test procedures (including description, identification and functional tests as relevant), as well as critical dimensions, technical drawings and photographs of primary and functional secondary packaging materials. The secondary packaging should be designed with consideration to the use and mechanical resistance of the DDC.
- Evidence of compliance with the relevant Ph. Eur. monographs, if applicable, and/or food contact Directives, as appropriate (such as declarations of compliance from suppliers).

P.8 Stability

Stability studies for the DDC should include the following tests/studies:

- Functionality tests (e.g. dose delivery per actuation, syringeability, communication with software, etc.). In case of complex DDCs, such as integral ingestible devices, additional functional tests related to the intended use of the medicinal product are required.
- In-use stability testing performed under the conditions of use as stated in the SmPC, unless otherwise justified.
- Microbial quality, sterility, content/potency and purity for the entire shelf-life and in-use period, as appropriate.
- Simulated transport studies that encompass chemical (e.g. degradation) and physical (e.g. vibration) stability, where relevant.

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

All materials of human or animal origin used in the manufacturing process of the DDC, or such materials coming into contact with the device during its manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section.

TSE agents

Where appropriate, a TSE statement confirming compliance of the component(s) of the DDC with EMEA/410/01 rev.3, to the European Standard “Medical devices utilising animal tissues and their derivatives – part 3 (EN ISO 22442-3:2007)” and Ph. Eur. 5.2.8 “Minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products” should be provided in this section.

Viral safety

Where applicable, an assessment of the risk to the DDC with respect to potential viral contamination should be provided in this section. The viral risk assessment should be made in accordance with the European Standard “Medical devices utilizing animal tissues and their derivatives – part 3 (EN ISO 22442-1:2015)” and Ph. Eur. 5.1.7 Viral safety.

For substances from human blood/plasma, compliance with relevant EU directives (the Blood directive 2002/98/EC and its associated technical 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 within the core dossier, as appropriate.

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

An index should be provided, which should cross refer to studies or information provided in 3.2.P and Module 5 sections as appropriate.

Section 3.2.R should include information related to demonstration of compliance of the device(s) with MDR Annex 1 (i.e. the applicable GSPRs) as follows:

1. Where available, an EU Declaration of Conformity issued by the device manufacturer, or a Certificate of Conformity issued by a NB that allows a CE mark to be displayed on the device.
2. If the above information on results of the conformity assessment is not available:
    (a) If the device is a class I device (excluding Im, Is, Irsi): the applicant's confirmation that the device part meets the relevant GSPRs, or
    (b) If the device is a class Im, Is, Irsi, IIa, IIb or III: an NBOp on the conformity of the device with the relevant GSPRs, issued by an appropriately-designated NB.
3. For medical devices that are used as container closure system for ATMPs, the applicant should provide evidence that the relevant GSPRs are met, as follows:
    (a) EU Declaration of Conformity issued by the device manufacturer, or
    (b) Certificate of Conformity issued by a NB, or
    (c) Confirmed by the applicant (e.g. by providing summary information in form of checklist).

Section 3.2.R may also include, if relevant, cross-reference to studies or additional information provided in 3.2.P sections.

Notified Body Opinion

Article 117 of the Medical Device Regulation (MDR) (EU) 2017/745 has introduced amendments to Annex I section 3.2 (12) of Directive 2001/83/EC concerning the documents that need to be submitted to CAs assessing MAAs for medicinal products incorporating a device as an integral part. These products are covered by the second subparagraph of Article 1(8) and the second subparagraph of Article 1(9) of the MDR.

Article 117 states (sic)…"*If the dossier does not include the results of the conformity assessment […] and where for the conformity assessment of the device, if used separately, the involvement of a notified body is required […], 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*."

The amended provisions of point 12 of Section 3.2 of Annex I to Directive 2001/83/EC, require applicants for MAAs of medicinal products incorporating as an integral part a device, 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. If the application dossier does not contain these results and where the conformity assessment of the device, if used separately, requires the involvement of a NB, the applicant is required to provide an opinion on the conformity of the device with the relevant general safety and performance requirements set out in Annex I to the MDR issued by a NB. It should be ensured that the NB is appropriately accredited for the issuance of such an opinion.

The processes by which a NB derives their opinion are not within the scope of this guideline; however, to facilitate review of the DDC, to enable both the assessor and applicant to determine how the NB opinion was formed, avoid duplication of assessment and identify aspects to be considered during the MAA, it is recommended that the NBOp is presented as a technical summary report. Annexes 1 and 2

provide guidance on the type of data to be included in the NBOp and propose a template to harmonise its format.

Usability (human factor) Studies

If the device has not been used in the proposed patient population before or if the setting of use is new and different from the intended use as confirmed by the certificate of conformity or NBOp (e.g. a prefilled syringe used for the first time in an outpatient setting or used for the first time in patients with conditions which could impair use), a usability study – to evaluate whether the DDC can be used safely to deliver the medicinal product to the target population - is expected. In this case, detailed information on usability and human factors studies (or justification for their absence) should be presented in Module 5, and a summary should be provided in Module 3.2.R (cross-referencing the detailed study in Module 5). In all other circumstances, a study summary should be presented in 3.2.R. This is considered a multidisciplinary topic and will also be reviewed outside of quality considerations.

Where evidence of usability is required, this may be supported by published and/or other relevant data for identical/similar devices on the market. However, if usability cannot be satisfactorily demonstrated in this way, a formal usability study is required to demonstrate usability of the medicinal product by the intended population. Applicants are encouraged to follow/use relevant harmonised standards to demonstrate compliance such as IEC 62366-1:2015 and IEC/TR 62366-2:2016.

Platform technology/technologies

Detailed information pertaining to the discussion presented in Section 4.3, should be presented in this section.

6. Non-Integral DDCs

The characteristics of non-integral devices used for the administration of medicinal products may impact the quality, safety and efficacy profile of the medicinal products. To the extent that administration devices are co-packaged with the medicinal product or, in exceptional cases, where the use of a specific type of administration device is specifically provided for in the Product Information of the medicinal product, additional information may need to be provided in the MAA on the characteristics of the medical device(s) that may impact on the quality, safety and/or efficacy of the medicinal product.

Requirements regarding quality aspects for non-integral DDCs are presented below. Given the broad range of non-integral devices, the information to be provided in this section will depend on the specifics of the device and the risks thereof to the quality, safety, and/or efficacy of the medicinal product. There are separate guideline sections for devices that are co-packaged and for those that are obtained separately and referred to in the product information.

6.1. Non-Integral DDCs with co-packed medical devices

6.1.1. Module 1, Product Information

Unless otherwise justified, where specific device(s) is (are) necessary for the correct use of a medicinal product and is (are) co-packaged with the medicinal product, the specific device(s) should be defined in the product information.

SmPC Section 4.2: The directions for proper use of the DDC should be described (including cleaning of the device as necessary), in line with relevant guidance. A device tradename may be stated.

SmPC Section 6.3: Information on the in-use shelf-life of the DDC should be provided, if relevant.

SmPC Section 6.4: DDC storage conditions should be listed.

SmPC Section 6.5: The type of the device(s) and its (their) component material(s) should be listed.

SmPC Section 6.6: Product-specific information should be provided for preparation or handling (including disposal of the device(s)).

Package Leaflet: Information should be consistent with the SmPC, provide clear and simple instructions on the intended use of the DDC for patients and/or for HCPs and be written in such a way as to prevent medication errors. Information related to the use of the device, consistent with the device IFU, if applicable, should be included.

Package Leaflet and labels: The outer packaging and the Package Leaflet may only include symbols or pictograms if necessary to clarify certain information compatible with the SmPC (e.g. instructions for use) which may be useful for the patient, to the exclusion of any element of a promotional nature.

6.1.2. Module 3.2.P, Drug Product

P.1 Description and Composition

A brief description and function of any device(s) used to administer the DDC should be stated.

P.2 Pharmaceutical Development

It is expected that the use of a medicinal product with a specified device is demonstrated to be safe and effective. This section should summarise relevant Quality information for the device including safety and performance, in the context of the device reproducibly delivering the required dose of the medicinal product within the intended use. This section should provide evidence for the suitability of the device(s) in its (their) intended use, provide a clear narrative of device and medicinal product development, and provide all relevant data (including justification of any new device, pharmaceutical form or excipient, etc., not previously used, where relevant). The amount of information provided in this section should reflect the risk of the device to impact the quality, safety and/or efficacy of the medicinal product.

A brief description of the device, and of the functionality of the device, together with the medicinal product, should be provided. It 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 expected).

P.2.1 Components of the Drug Product

A high-level description of the devices(s)/DDC should be provided.

P.2.2 Drug Product

A general discussion on the choice of device should be provided, including the intended use (usability), 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 intended 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, where relevant.

P.2.5 Microbiological Attributes

For medicinal products intended to be used sterile, the sterility of the non-integral device should be verified (e.g. by reference to the CE certificate). Maintenance of sterility throughout use and shelf-life of the final medicinal product should also be demonstrated.

P.2.6 Compatibility

Unless otherwise justified, compatibility between device and drug product throughout use and shelf-life of the DDC 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.
- 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

Although in the non-integral DDC setting, the device is not part of the container closure system, 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 identification number of the device). The specification applied to the incoming device upon receipt by the drug product manufacturer should be presented. For further details, reference should be made to the information in 3.2.R, including evidence of the CE mark.

P.8 Stability

If relevant, in-use stability data should be provided for the drug product in contact with the device, including device functionality that may impact the quality, safety and/or efficacy of the medicinal product.

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

If self-declared, the requirements for 3.2.A.2 as for the integral DDCs should be followed. Otherwise, a valid NB Certificate of Conformity can be accepted as evidence of compliance with EU requirements.

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

An index should be provided, which should cross refer to studies or information provided in 3.2.P sections as appropriate.

An EU Declaration of Conformity issued by the device manufacturer should be provided as evidence of the CE-mark. For devices of risk classes above Class I (i.e. Im, Is, Irsi, IIa, IIb and III) an NB Certificate of Conformity should also be provided.

Where applicable, and depending on the complexity of the device, any changes implemented in the design of the device during the development of the medicinal product should be discussed in terms of the impact on product performance characteristics (e.g. delivered dose, needle penetration force for subcutaneous/intramuscular injection and other usability factors). Appropriate data should be provided to demonstrate and justify the similarity of the overall performance during clinical phases with that after approval.

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 - that the device/medicinal product can be used safely to deliver the required dose to the target population – is expected. Where evidence of usability is required, this may be supported by published or other relevant data for identical/similar devices on the market. However, if usability cannot be satisfactorily demonstrated in this way, a formal usability study is required (see also Section 5.4).

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

Discussion of, and justification for the use of platform devices should be included in this section (for further detail, see Section 4.3 above).

6.2. Non-Integral DDCs with separately obtained devices

This section explains the data requirements that should be provided as part of MAA for medicinal products in the following scenarios:

- ATMPs, where devices used during surgical procedures for application, implantation or administration of the product, may have an impact on its efficacy or safety.
- In exceptional cases where the use of a specific medical device is provided for in the SmPC of the marketing authorisation because of the impact thereof on the quality, safety and/or efficacy profile of the medicinal product.

The impact of the specific device on the medicinal product (when used together) should be addressed using a risk-based approach, with consideration as to the need for a usability study. This should be documented in 3.2.P.2. If a separately obtained device referred to in the product information is used, then there must be evidence of efficacy and safety/bioequivalence for the medicinal product in combination with the device.

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

In section 3.2.P.2, it is expected that data on compatibility, dosing accuracy, handling, manipulation etc. are presented as appropriate.

In section 3.2.P.8, it is expected that in-use stability data are presented, if applicable.

Information on usability and human factors studies should be presented, unless otherwise justified (see Section 5.4 above).

7. Bridging to devices used in clinical development

Given the (often) critical contribution that a device makes to the safe and effective administration of a drug product, it is expected that the device be as advanced as possible in the development process (i.e. meets the relevant GSPRs) by the time pivotal clinical trials start.

While authorisation of clinical trials is a national issue and outside the remit of this guideline, in the context of the MAA, the following guidance is provided:

- Integral DDC: there is no requirement for evidence of compliance with the relevant GSPR to be provided for devices within integral DDCs used in clinical development. It is expected that the impact of any changes in devices during the pivotal clinical trials be described, evaluated and justified in terms of any potential impact of the changes on the quality, safety and efficacy of the medicinal product, from the beginning of the pivotal trials to the product that is proposed for market in the MAA. Where changes are made to the device, data to bridge the different device designs from a safety and efficacy perspective may be required in Modules 3 and 5. A risk assessment should be included in Module 3.2.P.2.4, which should describe the changes, batches used and trial(s) affected, and what mitigation was performed to minimise the impact on product quality.
- Non-integral DDC: where (device) clinical investigations were incorporated into the pivotal DDC clinical trial, because of their relevance to the MAA and because they could not be separated from the investigation of the medicinal product, the rationale for this approach should be discussed and justified in Module 5.

8. Lifecycle Management

A change listed in the variation guideline will require a variation of the appropriate category to be submitted to the medicines CA(s). All changes to medical devices and/or device components within DDCs should be presented in accordance with the relevant EU Variations Regulation and associated variation guidelines in place and should be submitted under the appropriate category.

Depending on the nature of the change, the MAH should consider whether updates to relevant documentation (e.g. NBOp, Declaration of Conformity, CE mark etc.) associated with the device in question are required to support the change.

The category of variation should take into consideration the impact of the change, e.g. a change to a device that impacts any DDC CQAs and/or any element(s) of the overall DDC control strategy may be considered a higher category of variation. 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 MA is consulted to agree the category prior to submission of the variation application.

Additional considerations

In cases where a variation is submitted to change or replace the device of a DDC, consideration should be given to whether there is an impact on the instructions for use between current and proposed devices, and any potential risks of user or medication error. The overall risk assessment of the DDC should be updated accordingly. Consideration should be given to the following:

- Communication plans may be needed in order to make patients and/or HCPs aware of the change.
- Timing for when the applicant plans to make the updated DDC available should be clear and justification for how long the currently registered DDC will remain on the market should be given, if required.
- If the instructions for use are different between current and proposed devices, the potential risks of user error and the potential for medication errors, should be considered. The risks may be due to familiarity with previous device instructions, complexity of new/revised device(s), etc. Human Factors/usability studies may be required.
- If there is a risk of a medication error because of the introduction of a new/revised device(s), this may need to be captured in the Risk Management Plan (RMP).

9. Emerging Technologies

It is recognised that developments in science and technology for medical devices may advance more rapidly than for medicinal products alone. This guideline provides basic requirements to be expected in a quality dossier for an MA; it is recognised that alternative approaches for emerging technologies could be followed, if adequately justified.

If the DDC will be utilising emerging technologies, it is recommended to engage with medicines CAs in a timely manner, e.g. by formal scientific advice, or through Innovation Offices, etc. It is also recommended to identify and engage in discussions with a NB in a timely manner.

The provision of a sample or samples of the DDC to the assessors in order to simulate use is strongly encouraged to aid assessment and minimise queries relating to hands-on, practical aspects of its use.

10. Definitions

Applicant

The commercial entity responsible for the marketing authorisation application of the DDC in the EU.

Control Strategy (as per ICH Q10)

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 and drug product materials and components, 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 components that together contain and/or protect the medicinal product, including devices, as defined in Section 1 of this guideline.

Dossier

The complete body of data submitted for regulatory review. In this case, the dossier relates to the administrative and quality components of the (e)CTD, i.e. Module 1 (administrative), Module 2 (Overall Summaries) and Module 3 (quality) respectively, and typically specifically in relation to the content of Module 3.

Drug-Device Combination Product (DDC)

A medicinal product(s) with integral and/or non-integral medical device/device component(s) necessary for administration, correct dosing or use of the medicinal product. For specific examples of the definition as interpreted for this guideline, see Section 1, above.

Drug Product Manufacturer

The commercial entity legally responsible for manufacture of the integral or non-integral (co-packaged) DDC.

Device Manufacturer

The commercial entity manufacturing and supplying sterile/non-sterile devices and/or components to the drug product manufacturer for incorporation into the DDC.

Marketing Authorisation Holder (MAH)

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

Medical Device (synonyms: Device, MD)

A device that fulfils the definition of Article 2(1) MDR and is intended to be placed on the market, made available on the market or put into service in the EU.

Medical device component

A device that fulfils the definition of Article 2(1) MDR, where it is considered a constituent part of a marketing authorisation (integral or non-integral). It is synonymous with medical device.

Medicinal Product (synonyms: MP, Drug Product, DP)

Refer to Article 1(2) of Directive 2001/83/EC.

Notified Body Opinion (NBOp)

An opinion provided by a Notified Body on the conformity of the device component(s) of an integral DDC with the relevant GSPRs set out in Annex I of Regulation 2017/745, as required by Article 117 of the MDR. Refer to Annexes 1 and 2 of this guideline for a proposal of a NBOp template and associated documentation.

Performance

The action of the medical device in performing its intended function.

Platform technology

A technology that has already been approved for another medicinal product and has therefore been (at least partly) characterised previously.

Usability

Evidence that the DDC can be used safely to deliver the medicinal product to the target population. This is also known as human factors engineering and/or usability engineering.

Abbreviations

(c)ATMP	(combined) Advanced Therapy Medicinal Product
CE	Certificate European
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
CS	Control Strategy
DDC	Drug-Device Combination product
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
GSPR	General Safety and Performance Requirement
HCP	Healthcare Professional
ICH	International Council for Harmonisation of Technical requirements for Pharmaceuticals for Human Use
IFU	Instructions for Use (device)
ISO	International Organisation for Standardization
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MDR	Medical Device Regulation (EC 2017/745)
MPD	Medicinal Products Directive (2001/83/EC, as amended)
NB	Notified Body
NBOp	Notified Body Opinion
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
Q&A	Question and Answers
SmPC	Summary of Product Characteristics

Annex 1: Proposal for Notified Body Opinion template

NB logo
NB name and address
NB number

Notified Body Opinion
(Article 117 of the Medical Device Regulation (EU 2017/745)

Compliance of device(s) incorporated into an integral drug-device combination product
with
Annex I (General Safety and Performance Requirements)
Medical Device Regulation (EU 2017/745)

Administrative reference number: _____
(including version number)

Reviewer name and position: _____

NB authorisation (signature): _____

Authorisation date (YYYY/MM/DD) _____

I. SUMMARY OF NOTIFIED BODY OPINION

<Clearly state opinion i.e. acceptable or not acceptable>

<Include a brief summary highlighting the basis of the opinion, with any relevant constraints or other considerations>

II. LIST OF ABBREVIATIONS

<Insert list of abbreviations>

III. ASSESSMENT OF THE GENERAL SAFETY AND PERFORMANCE REQUIREMENTS (GSPR)

a. Basis of assessment, Article 117 of Regulation EU 2017/745.

In consideration of the following text from Article 117 of the Medical Device Regulation (EU 2017/745), [sic]… "Where, 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 (GSPR) 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."

b. General Drug-Device Combination product information.

<Summary information to ensure mutual understanding of the product under assessment including a detailed description of product, in particular the device component(s) indications, method of administration, intended use, etc.>

c. Scope of assessment

<List of applicable GSPRs, with justification for any omissions>

d. Assessment

<This should form the main body of the report>

<For each applicable GSPR, summarise the data presented, and final outcome(s) of the assessment>

<Any changes made to the device during pivotal clinical trials should be described (changes, timelines) and the impact on relevant GSPRs discussed>

e. Notified Body Opinion

<Clearly state the opinion and a summary of the justification for the NB opinion>

IV. REFERENCES

<List relevant references, including ISO standards>

Annex 2: Template cover sheet for Notified Body Opinion

It is intended that this document is completed in two situations:

1. Where an application is made for a stand-alone medicinal product. In this case, the MAH completes this section.
2. Where an application is made that utilises a platform technology. In this case, it is the technology owner who completes this section, effectively providing a letter of authorisation to the MAH to use the data, similar to the approach used where a CEP holder authorises the use of the active substance in an EU procedure.

GENERAL INFORMATION

PRODUCT DETAILS	
Invented / Trade name of the medicinal product	**<as per MAA>**
Applicant	**<Name and address of MAH i.e. legal entity holding the MA>**
Marketing authorisation type	**<e.g. Centralised application>**
Marketing authorisation procedure number	**<e.g. ….>**
Pharmaco-therapeutic group (ATC code)	**<e.g. D08A C52>**
Indication(s)	**<As per SPC4.1>**
Pharmaceutical form(s) and strength(s)	**<e.g. 10mg, 20mg INN solution for injection, pre-filled syringe>**
INN (or common name) of the active substance(s):	**<as per MAA>**
Authorisation to use NBOp	**<Suitably authorised / signed by either the MAH, applicant or the platform technology holder>**