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Best Practice Guide for clinical trials with integral drug-device combination products including change control and usability studies

Medtech & Pharma Platform, Working Group on Combined Products, December 2020

Introduction

With the date of application of the new Medical Devices Regulation (MDR, EU 2017/745)[1] in the European Union (EU) on the horizon, marketing authorization applicants for integral Drug-Device Combination products (integral DDC) are faced with a number of topics requiring further guidance.

One topic requiring clarification is the expectation on usability and clinical evidence from integral DDC clinical trials to support the assessment of the General Safety and Performance Requirements (GSPRs) and benefit-risk ratio determination.

This topic is of particular importance under the MDR since it impacts the evidence to be presented in support of a Notified Body Opinion (NBOp) and preparation of Marketing Authorisation Application (MAA).

The objective of this guide is to present the current best practice of Medtech & Pharma Platform (MPP) Association member companies on the usability and clinical data requirements for medical devices component of integral DDC.

The first part of this best practice guide focuses on the clinical data for integral DDC and changes to the medical device component during pivotal clinical trials.

The second part of this best practice guide focuses on benefit-risk ratio and usability studies for integral DDC.

[1] REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 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

Scope of this best practice guide

Territory	European Union
Products	Device constituent component of integral DDC, i.e. devices intended to administer a drug, where the drug is placed on the market in such a way that they form an integral product which is intended exclusively for use in the given combination and which is not reusable.[2] Examples: single dose pre-filled syringes, pens and injectors.
Regulatory schemes	The leading scheme is the Medicinal Products Directive (Directive 2001/83/EC; MPD), with the amendment of the MPD by Article 117 of the Medical Devices Regulation (Regulation (EU) 2017/745; MDR), the relevant General Safety and Performance Requirements (GSPRs) of Annex I of the MDR must be fulfilled.

Points to consider for integral DDC clinical trials

When assessing the clinical data needs of the device component of the integral DDC, the marketing authorization applicants should consider the requirements outlined in the MDR Annex I General Safety and Performance Requirements (GSPRs); particularly GSPRs 1, 3 (c), 6, and 8 in relation to the benefit-risk ratio determination and patient/user safety.

All device constituent parts of integral DDC have to fulfil the relevant GSPRs for the NBOp[3] (and MAA) in accordance with the MDR Article 117 as of 26 May 2021, the date of application of the MDR. In general, all relevant GSPRs related to the benefits, risks and safety of the device constituent part for users, patients and other persons shall be duly substantiated and a benefit-risk determination shall be documented in the MAA.

Clinical evidence derived from integral DDC clinical trials can be used to substantiate the safety and benefit-risk ratio assessment of the device constituent part, and in particular GSPRs 1, 3(c), 6 and 8. It is relevant to note that the MDR does not specifically require a clinical evaluation for device constituent parts of integral DDC with a pharmacological principal mode of action. Other sources of relevant evidence in support of the safety and determination of the benefit-risk ratio can be for example technical testing, risk management, human factors/usability studies, and already published relevant clinical data.

All GSPRs relate to the benefits and risks of the device part of the DDC. Nevertheless, GSPRs 1, 3(c), 6 and 8 are specifically related to the benefit-risk ratio determination and, as part of Annex I Chapter I "General Requirements", applicable independently from the type of device[4]. These requirements focus on the device performance based on the intended purpose, on the benefit-risk ratio and on the health and safety of the patient/user and thus are directly connected to clinical data.

[2] MDR, Article 1(9), 2nd subparagraph
[3] CE-mark devices part of integral DDCs are not required to obtain an NBOp.
[4] if not stated otherwise, as in case of GSPR 9

Although clinical trials for integral DDC are conducted first and foremost in accordance with requirements for drugs, also medical devices' requirements need to be considered to ensure that the relevant GSPRs are fulfilled. In this regard, the following documents provide helpful guidance:

- EN ISO 14155: 2012 / ISO 14155:2020 Clinical investigation of medical devices for human subjects – Good clinical practice
- MEDDEV 2.7/1 Rev.4: Guidelines on medical devices - clinical evaluation: A guide for manufacturers and Notified Bodies under Directives 93/42/EEC and 90/385/EEC[5]

Note that these documents are generally applicable to products regulated as medical devices, whereas integral DDCs with pharmacological mode of action are regulated in the EU as drugs. They can, nevertheless, be helpful in assessing the clinical data needs for integral DDCs.

The EN ISO 14155 standards focuses on the assessment of "the safety or performance of medical devices for regulatory purposes". This standard is connected to the requirements that are outlined in GSPRs, such as GSPR 6.

MEDDEV 2.7/1 Rev.4, on the other hand, provides guidance on which Essential Requirements are addressed by a clinical evaluation - Directive 93/42/EEC (Medical Device Directive; MDD) Annex I, sections 1, 3, 6. These sections correspond to the GSPRs considered:

- GSPR 1 is based on MDD Annex I sections 1 and 3
- GSPR 8 is based on MDD Annex I section 6

Moreover, the guideline also describes which documents/data need to be aligned to ensure conformity to the Essential Requirements (ERs) of the Medical Devices Directive (MDD, 93/42/EEC) and thus under MDR conformity with the GSPRs and which topics are important for the evaluation of sufficient clinical evidence which are in focus of a Notified Body's assessment.

It is worth noting that a clinical evaluation as such is not required by the MDR for integral DDCs with a pharmacological principal mode of action. Thus, the guidance documents above can be consulted when developing a device constituent part of an integral DDC, although it is not obligatory to follow them.

[5] MDCG 2020-5 "Guidance on clinical evaluation - equivalence" outlines that MEDDEV 2.7/1 rev.4 also remains relevant under the MDR ("The European Commission has published a guide on clinical evaluation under the Directives 93/42/EEC and 90/385/EEC; MEDDEV 2.7/1 rev.4. This MEDDEV guide should be used also during the process of demonstrating equivalence under the MDR.")

Changes in device constituent parts of integral DDC

In assessing changes to the device constituent parts of integral DDCs from the start of pivotal clinical trials, EMA's "Guideline on the quality requirements for drug-device combinations"[6] should be considered, in particular its section 7":

> *Section 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, the device 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)* ***start****.*
>
> *While authorisation of clinical trials is an issue within the competence of the national authorities hence outside the remit of this guideline, in the context of the MAA the following guidance is provided: for both integral and non-integral DDCs, the impact of* ***any changes in devices during the pivotal clinical trials should be described, evaluated and justified*** *in terms of any potential impact on the quality, safety and efficacy of the drug,* ***from the beginning of the pivotal trials to the product that is proposed to be placed on the market*** *in the MAA. Where changes are made to the device, data to bridge the different device designs from a quality, safety and efficacy perspective may be required. 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.*

A key point in section 7 of the guideline is about the expectations on management of changes to the device (parts). In this best practice guide, we focus on the management and documentation of changes and their relevance for the MAA preparation.

This is also relevant for the NBOp when any data from clinical trials that will be used to support conformity to the GSPRs is obtained with a device constituent part which is subject to a change after the beginning of pivotal clinical trials.

[6] EMA / CHMP / QWP / BWP/259165/2019 ("Guideline on the quality requirements for drug-device combinations" (Draft version April 8 2020)

The following table outlines MPP's interpretation of the EMA guideline:

Impact assessment on any change(s) to device constituent parts	
Starting point	Beginning of pivotal trials
End point	Product presented in MAA to be placed on the market
Assessment	Impact of the device constituent part change on the quality, safety and efficacy of the drug
Evidence	Documented objective evidence: • Description of the device constituent part change(s) • Evaluation of the device constituent part change(s) • Justification of the device constituent part change(s)

In integral DDCs, the product consists of a drug constituent part and a device constituent part. The EMA guideline outlines the importance of adequate documentation on change(s) performed on the device constituent part and focuses on the impact on the drug.

Thus, changes need to be regarded from two angles:

1. Impact of the change on the device constituent part's quality, safety and performance
2. Impact of the change on the drug constituent part's quality, safety and efficacy

The introduction of MDR Article 117 includes also Notified Bodies' role to assess the impact of changes on the device constituent part's quality, safety and performance.

The Notified Body either evaluates the technical documentation of the device constituent part (in case the device constituent part is a CE marked medical device) or evaluates the conformity of the device constituent part with the relevant GSPRs set out in Annex I (NBOp).

In either case the documentation on fulfilment of the (relevant) GSPRs as defined in Annex I is assessed by the Notified Body for all device constituent parts higher than Class I (Class Is/Ir/Im/IIa/IIb or III).

The second key aspect of Section 7 of the guideline is the evaluation of bridging data needs in case of a change to the device part during pivotal clinical trials.

The following table outlines MPP's interpretation of the guidance in such cases:

Bridging data on the device constituent parts	
Starting point	Beginning of pivotal trials
End point	Product presented in MAA to be placed on the market
Assessment	Data (e.g. test reports), i.e. documented objective evidence that demonstrate that quality, safety and efficacy of the drug were not affected by the device constituent part change(s) performed
Evidence	Documented objective evidence: • Description of the device constituent part change(s) • Description of the batches used • Description of the trials affected • Description of the mitigation measures (if any) applied to ensure that the impact of the device constituent part change(s) on the product quality was minimal
MAA module	In Module 3.2.P.2.2

As a consequence, it is the view of MPP that the relevant GSPRs should be included in the change impact assessment, as well as in the change performance in relation to the device constituent part.

Moreover, additional verification and/or validation activities may result from the change(s) and thus should be considered in the assessment, as well as the potential need to collect additional (bridging) clinical data.

Finally, the impact on the device constituent part's technical documentation should be assessed and updated accordingly based on the change(s).

Benefit-risk ratio for integral DDC and usability studies

The benefit of the device constituent part of an integral DDC must outweigh the risks associated with its intended purpose. When assessing such a device constituent part, data from the following sources play a major role and provide the basis for the final assessment of benefit versus residual risks of the device constituent part of the DDC:

- literature search;
- market data (e.g. known use problems, safety databases) of equivalent devices;
- outcome of a use-related risk analysis (according to ISO 14971);
- any data from usability studies (formative and/or summative) as well as relevant user experience from previous clinical trials

Some device constituent parts do not have any novel features and are considered well-established integral drug delivery devices, as they have already been placed on the market in large volumes and for a number of years (e.g., prefilled syringes). For such devices, dependent on the outcome of the use-related risk analysis, a formative and/or summative usability study may not be necessary.

However, when the device constituent part of the integral DDC presents novel features and/or, is intended to be used in new user groups and/or novel therapy and/or with novel outer packaging, a formative and/or summative usability study might be required, and thus becomes part of the documentation reviewed and assessed by Notified Bodies in the NBOp or CE marking process.

In the case of a significant design change of a well-established device constituent part of an integral DDC, a summative usability study might become necessary as well. In line with IEC 62366-1, a justification is always required if a summative usability study is not conducted. Such a justification would be based on already existing usability studies, known use problems, task analysis, instructions for use (IFU) comparability to marketed products and a demonstrated very good understanding of the user population and the use environment. That information needs to be considered and consolidated in a comprehensive use-related risk analysis (according to ISO 14971) and ensuing usability summary report.

Demonstration of conformity to the relevant GSPRs related to benefit-risk ratio for the device constituent part of the integral DDCs can be achieved by several means and not just by usability studies. Alternatively, a well-justified and documented risk based approach based on data from literature research, safety databases, market data of equivalent devices and use-related risk analysis, can be used to show that implemented risk control measures are effective and no further verification/validation (usability studies) are necessary.

In case of clinical trials of an integral DDC, the device constituent part (e.g. pre-filled syringe, auto-injector) must be safe to use and perform as intended (i.e. be effective). In this context, a preliminary assessment of the benefit-risk-ratio should be established and documented before starting the first clinical trial with the integral DDC.

The assessment needs to cover the final design intended to be placed on the market when it comes to the preparation for the Notified Body conformity assessment (NBOp or CE marking) and preparation of the MAA.

Depending on the following characteristics of the device constituent part, usability studies may need to be conducted already before the first use in clinical trials, parallel to the early stage of development of the integral DDC, at a later time-point (but ideally prior to Phase III) or not at all. To determine the appropriate course of action the following questions could be of help:

- Is the device a well-established, off-the-shelf device/device components, or is it a novel device/device component;
- What are the conditions of use (e.g. use by healthcare professional (HCP) or lay person);
- What is the use environment and characteristics of the user population(s);
- Patient needs, indication and others.

The necessary timing, content and scope of the eventual study, as well as number and type (i.e. formative and/or summative studies), are defined by the respective situation and identified risks as outcome of the risk management process according to ISO 14971.

Best practice recommendations

The goal of this best practice guide is to provide recommendations regarding the clinical data and to ensure compliance by design with requirements for the device constituent part of integral DDCs, and to ultimately enable smooth and on-time reviews by EMA, National Competent Authorities, and Notified Bodies. Our recommendations regarding clinical data and usability studies for integral DDCs are as follows:

1. Setup of DDC clinical trials including device parts
    - Assess which GSPRs applicable to the DDC can and maybe need to be supported by data from integral DDC clinical trials. Consider particularly the benefit-risk ratio and the safety and performance of the device constituent part, especially in relation to GSPRs 1, 3 (c), 6, and 8;
    - For guidance on how to enhance data collection on the device constituent part to support the evaluation of performance, safety and benefit-risk ratio, consider using EN ISO 14155 and MEDDEV 2.7/1, Rev.4 as appropriate and practicable;
    - Ensure availability of all necessary data on the integral DDC for the NBOp so that it can be used in direct or indirect support of device performance, safety and benefit-risk evaluation.
2. Setup and/or update of a change management system related to changes in devices during and following drug-based clinical trials
    - Assess the impact of device changes during pivotal clinical trials, with a focus on the potential impact on the quality, safety and efficacy of the drug;
    - Perform adequate verification and collect sufficient bridging data to evaluate the impact of changes during pivotal clinical trials, in line with EMA / CHMP / QWP / BWP/259165/2019 ("Guideline on the quality requirements for drug-device combinations" (Draft version April 8, 2020);
    - Adequate connection of changes performed to additional testing activities required including update of documentation.
3. Assess and decide on need of usability/human factors study (-ies)
    - Case-by-case assessment of whether usability studies are required or not;
    - When a usability study is not performed, provide a justification in line with IEC 62366-1.

We are looking forward to working with relevant stakeholders creating a proportionate regulatory framework for combined products in Europe.

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About the Medtech & Pharma Platform Association

The Medtech & Pharma Platform Association (MPP) draws together companies from the pharmaceutical, medtech and ICT sectors and provides opportunities to exchange knowledge and collaborate in technology and regulatory areas related to combined products.

The MPP's objectives are:

- To enhance synergies between the pharma, medtech and ICT industries
- To establish new collaboration models to ensure and accelerate market access for safe and innovative treatment options
- To support government and regulators in developing a balanced and proportionate regulatory and political framework for combined products including connected combined products

MPP member companies include: SFL Regulatory Affairs & Scientific Communication, Swiss Medtech, Ypsomed, Novartis, Merck Sharp & Dohme, Sanofi, anteris helvetia, Aquilon, Edwards Lifesciences, Philips Innovation Services, Covance, Boehringer Ingelheim.

About the MPP Working group on combined products

The MPP Working Group on combined products aims to facilitate dialogue between key stakeholders with a view to jointly develop robust and flexible regulatory instruments. These instruments can include best practices and guidelines that allows for a dynamic adaptation of the regulatory framework to promote innovation and maximize patient safety.

The MPP intends to share the Best Practice Guide with all relevant regulating bodies and actors at EU level with the aim to establish a constructive dialogue in order to find viable solutions to better regulate these products.

We are looking forward to working with relevant stakeholders creating a proportionate regulatory framework for combined products in Europe.