European Federation of Pharmaceutical Industries and Associations



Reflection Paper

The challenges of integrating Medical Devices (MDs) into medicinal product clinical trials - CTA Documentation

EFPIA Reflection Paper on technical documentation requirements for medicinal product Clinical Trial Applications with MDs

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LIMITATIONS

Importantly, the European Commission has launched the so-called 'COMBINE' project in June 2023 aiming at clarifying 'Combined studies'. This project involves the simultaneous investigation (i.e. combined use) of a medicinal product and an In Vitro Diagnostic (IVD) and/or an MD (MD) which are subject to the requirements of both the EU Clinical Trials Regulation (CTR) and the In Vitro Diagnostic Regulation (IVDR) or MD Regulation (MDR), respectively. In the analysis phase, more than 70 issues that constrain new medicinal product development and clinical studies in Europe were identified. This paper focuses on one issue raised by EFPIA, classified as frequent and critical, and accepted by the COMBINE project governance in its 'Analysis report', recorded as issue n°78: The need for harmonized interpretation of the CTR and European Medicines Agency (EMA) guidance at the interface of the MDR for a clinical trial of a medicinal product using an MD that is not investigated while it is non CE-marked, or CE-marked but used outside of its intended purpose.

Finally, this reflection paper represents an industry association perspective and does not confer any legal aspect, nor any immunity to its user (Person or Legal Entity). The perspective is built on the study of the regulation, industry discussion, and consensus, and is not set in stone or agreed upon by the Regulators (EMA, Competent Authority MD (CAMD)) at this time.

EXECUTIVE SUMMARY

A cross-industry working group within EFPIA has recently focused on European specific topics relating to clinical trial applications (CTA) when the medicinal product is delivered with an MD.

Sponsors currently face inconsistent interpretation of which medicinal product clinical trials will require a clinical investigation application (CIA) under the MDR requiring a separate regulatory device related filing. It is highly desirable that the documentation is kept in one complete application covering both the medicinal product and the medical device. Investigational Medicinal Products (IMPs) are frequently delivered in clinical studies using MDs that are either CE marked but used outside of their intended purpose, or non-CE marked. Digital health technology (DHT) used to measure endpoints in medicinal product trials often qualifies as a MDMD. This paper provides an Industry perspective on the criteria and a risk-based approach that would support an Investigational Medicinal Product Dossier (IMPD) filing under the CTR containing relevant product quality information and data pertinent to the assessment of the MD used, for example, to deliver the medicinal product when the device is not investigated in the study. The proposal is illustrated with five case studies in the Appendix of this reflection paper.

The scope of this reflection paper does not include IVDs however it does include all types of investigational MDs. Therefore, two case studies of MD Software (MDSW), which is regulated by MDR 2017/745, have been included.

This reflection paper outlines how existing EMA quality guidance (EMA/CHMP/QWP/BWP/259165/2019) can be used to show compliance to relevant safety and performance requirements and seeks to demonstrate that, with an 'in depth' understanding of the MDMD intended purpose as determined by the MD manufacturer, a safe and effective use of the MDMD can be guaranteed for the specific clinical study purpose. In the opinion of EFPIA, this proposal aligns with MDCG 2021-6 Questions & Answers regarding clinical investigation, Annex III and

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complements Annex I of MDR 2017/45. However, the close interplay between demonstration of benefit/risk for the medicinal product and safe and effective use of the MDMD make it highly desirable that the quality requirements are harmonized between EU member states (MS) and the documentation is kept in one complete application, even if a separate CIA under EU MDR is justified. Sufficient expertise within the Health Authorities for their review, i.e., a coordinated review and assessment of device documentation of compliance with safety and performance requirements together with the CTA documentation, is highly desirable to ensure integrated review pathways.

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List of Abbreviations:

Abbreviation	Description
CAMD	Competent Authority MD
CIA	Clinical Investigation Application (Devices)
CMS	Concerned Member State
CTA	Clinical Trial Application (medicinal products)
CTD	Clinical Trials Directive
CTIS	Clinical Trials Information System
CTR	Clinical Trial Regulation
DDC	medicinal product Device Combination
DHT	Digital Health Technologies
EC	Ethics Committee
eCTD	electronic Common Technical Dossier
EFPIA	European Federation of Pharmaceutical Industries Association
EMA	European Medicines Agency
ERAO	European Regulatory Affairs and Operations
EU	European Union
EUDAMED	European Database on MDs
GSPRs	General Safety and Performance Requirements
IB	Investigational Brochure
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IVD	In vitro diagnostic
MAA	Marketing Authorization Application
MD	MD
MDD	MD Directive
MDR	MD Regulation
MDSW	MD Software, an EU terminology similar to the more internationally (IMDRF and US) used SaMD denomination (Software as MD)
MP	Medicinal Product
MQEG	Manufacturing and Quality Expert Group at EFPIA
MS	Member State
NCA	National Competent Authority (For medicinal product)
QTPP	Quality Target Product Profile (As per ICH Q8 definition)
RMS	Reference Member State

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1. SCOPE AND OBJECTIVES

MDs are frequently used in medicinal product (drug) clinical studies. As medicinal products and MDs are covered by different regulatory frameworks in Europe, situations where a not CE-marked but fit for purpose MD is used in a medicinal product clinical trial leads to regulatory documentation challenges.

This may specifically occur when:

- The device used in the study is CE marked but is used outside of the conditions covered by its approved intended purpose in the clinical study. The clinical study does not include device specific performance or safety endpoints, in other words the device including ancillaries, where applicable, is not intended to be investigated in the medicinal product clinical trial with the intent of supporting a MD conformity procedure.
- MD software (MDSW/DHT), often (still) non-CE marked, is used in a clinical study to measure an endpoint, to provide diagnostic or therapeutic information for facilitating the conduct of the trial. Regulatory challenges (e.g. about the applicable regulatory pathway) can arise even if the MDSW/DHT has general safety and performance data, including verification and validation, demonstrating it is fit for purpose and low risk for the specific study (according to MDCG 2021-4).

This document addresses submission and review challenges for standalone MDs and/or MDSW/DHT used in CTAs when the aim of the clinical study is not to generate device safety and performance data for future MD conformity assessment procedures or for future label claims. The five examples included in the case study section are given for different medicinal product/device or medicinal product/MDSW combinations.

For ease of reading, the terminology 'device' or ' MD are used synonymously in this paper and include MDSW. When distinguishing between both categories of devices helps to clarify the reflection, then both MD and MDSW terminologies are used in the text.

It is the industry view that the scenarios developed in this reflection paper should not require an additional CIA for the respective delivery which is the current standard scenario in Europe for such a situation. It is of interest to all stakeholders to allocate resources only to clinical investigations of devices for which data are needed to support the conformity assessment process instead, while addressing the aforementioned scenarios through an integrated CTA under medicinal product law, which also covers the qualification of the MD as a tool to facilitate the study. It is left to the to define the required documentation which appears to be not consistent among the National Competent Authorities (NCAs and CAMDs). Pharmaceutical companies have frequently experienced this when the device used in the planned studies will not be used to obtain any clinical data related to the device.

Objectives:

- Present the problem statement, a high-level overview of the current CTR regulatory pathway for CTAs as well as the EFPIA survey results demonstrating the challenges faced by Industry for CTAs using MDs.
- Inform key decision makers about the pharmaceutical industry's concerns regarding the regulatory challenges on the quality documentation requirement for the CTA using MDs and/or MDSW/DHT

mainly due to inconsistencies in EU national expectations and/or different interpretations of EU MDR 2017/745 and EMA/CHMP guidelines.

- Propose a common understanding on the applicability of the dual framework as well as the roles & responsibilities of the CTA Sponsor, the Health Authorities for medicinal product (HA) and the National Competent Authorities (NCAs) for MDs when reviewing and approving IMPD file for a CTA using MDs including MDSW/DHTs.
- Present five case studies to provide real-life examples of challenges and opportunities for harmonization of quality documentation requirements and thus efficiencies for industry and regulators.
- Present EFPIA's proposal for harmonized interpretation of the applicability of EU MDR 2017/745 Articles 62 and 82 at the interface of EU CTR 536/2014.

Out-of-scope:

- The single integral drug-device combination (iDDC), for which the medicinal product is the principal mode of action.
- Procedural aspects for combined CTA and Clinical Investigation Application (CIA) when both a medicinal product and a delivery device (regardless of the risk level) are investigated as part of one single clinical study.
- IVDs (as previously mentioned)

Further guidance and harmonization at a global level is needed on procedural aspects for CTA/CIA when both a medicinal product and a device are investigated as part of one single, combined clinical study. The current challenge has been identified and will be addressed by the COMBINE Program, launched by the European Commission in June 2023 (Ref 1).

It is EFPIA's recommendation to distinguish between combined CTA/CIA studies with the aim of generating clinical evidence for both an IMP and a MD, and one single CTA application for a clinical study without the purpose of generating MD data for a future conformity assessment of the MD.

Nevertheless, the EFPIA proposal considers the interface between CTR and MDR where clinical trials using a MD include the evaluation of device endpoints for the delivery device part of the DDC (not single integral); this indicates the need to follow either MDR Art 62 or 82 for clinical investigation purposes. This interface is illustrated with one case study with focus on MDSW.

To further facilitate the understanding of the approach developed, the definition of 'Intended purpose' per MDR article 2 Definitions is provided: *'Intended purpose' means the use for which a device is intended according to the data supplied by the manufacturer on the label, in the instructions for use or in promotional or sales materials or statements and as specified by the manufacturer in the clinical evaluation.'*

The following regulatory frameworks and guidelines are pertinent to the scope and objectives of this reflection paper:

- EU Medical Device Regulation (MDR) 2017/745;
- Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use (CTR), and repealing Directive 2001/20/EC;
- Clinical Trials Regulation (EU) N° 536/2014 Questions & Answers Version 6.9;
- EMA/CHMP Guidelines on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, reference EMA/CHMP/BWP/534898/2008 Rev. 2 - Committee for Medicinal Products for Human Use (CHMP) – 27 January 2022. (Note: A similar guideline

covers requirements on the chemical and pharmaceutical quality documentation of investigational medicinal products in clinical trials, reference EMA/CHMP/QWP/545525/2017 Rev.2 - Committee for Medicinal Products for Human Use (CHMP) – 27 January 2022);

- EMA/CHMP/QWP/BWP/259165/2019 - Guideline on quality documentation for medicinal products when used with a medical device;
- ICH Q8 (R2) Pharmaceutical Development;
- MDCG 2021-6 Questions & Answers regarding clinical investigation;
- MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR.

The following document is used in support of this reflection paper:

- EFPIA – Survey one 2023 – Impact of IVDR and MDR on clinical trials, results (see Table 1);
- Ref 10: Abou-El-Enein, M., Schneider, C. Deciphering the EU clinical trials regulation. *Nat Biotechnol* **34**, 231–233 (2016);
- Ref 11: Podhaisky H.-P., Digital Health Technology in European Clinical Trials, How to Improve the Status-Quo of the Regulatory Landscape? Ther Innov Regul Sci. 2024 Jul;58(4):610-613. doi: 10.1007/s43441-024-00657-y. Epub 2024 Apr 24. PMID: 38656468.EU Clinical Trial Regulation CTR 536/2014.

2. PROBLEM STATEMENT

In the EU, medicinal products and MDs remain regulated by separate legal frameworks. When clinical studies are conducted with an IMP using a co-packaged device that does not bear a CE-mark or that bears a CE-mark but is used outside of the claimed intended purpose, medicinal product study Sponsors face inconsistencies in national expectations with regards to the documentation to be provided for MDs. This situation arises because the requirements for MD documentation in drug clinical trials are not specified in the MDR and health authorities tend to determine their own local requirements for devices used in drug clinical trials (Ref 2).

In addition, given the Sponsor's aim is not to obtain clinical data for a separate device conformity procedure, the pharmaceuticalpharmaceutical industry questions the pertinence of applying in full MDR Article 62 or 82. The use of the MD being always linked to the assessment of applicable general safety and performance requirements, as per MDR Article 82 (1) cross-referencing MDR Article 62(4/l), the CTA Sponsor has the responsibility to provide assurance that these requirements are met prior to starting a clinical trial.

Nowadays, for the same application, sponsors face inconsistent interpretation of which clinical trials require CIAs for the MD used in the trial, and additional and different documentation requirements based on different MDR 2017/745 articles (*). If the MD is classed as an investigational device most Member States (MS) require two parallel applications: One for the medicinal product (Clinical Trial Authorisation, CTA under EU-CTR) and one for the device (Clinical Investigation Application, CIA, under MDR). The separate applications increase the risk of working in silos and missing key interface information for the safety and efficacy/performance of one or both products. Much of the information is common to both applications, for example the clinical study protocol, Ethics Committee (EC) considerations and administrative details. The medicinal product and the MD(s) are part

of “one development” and although different expertise might be required to review the drug and device aspects, it is important that one single application provides the entire picture.

Moreover, for MDR Article 82 section 2, it is stated that: *“…each Member State shall define any additional requirements for such investigations, as appropriate for each MS concerned.”* And indeed, it is EFPIA members' experience that these requirements can vary significantly from MS to MS as illustrated further in the case study section of this reflection paper.

This reflection paper investigates and proposes the potential solutions to the challenges highlighted moving towards one single CTA application.

(*) Case reported by EFPIA members in EFPIA survey (January 2023): For the same CTA, different member states asked for MDR Articles 62 (General requirements regarding clinical investigations conducted to demonstrate conformity of Devices), Article 74 (Clinical investigations regarding devices bearing the CE marking), or Article 82 (Requirements regarding other clinical investigations).

3. BACKGROUND: HIGH LEVEL VIEW OF THE CURRENT CTA REGULATORY PATHWAY

A high-level overview of the current regulatory pathway for CTAs according to the CTR (Ref 3) is presented in Figure 1 below. The focus of this paper is on the Part 1 assessment and the Investigator’s Brochure and Investigational Medicinal Product Dossier (IMPD). Specifically, in the IMPD, the performance and safety data as it pertains to the device aspect of the clinical trial are addressed. Part 2 information covers the general country specific aspects of the clinical trial and is dependent on the content of Part 1. The primary objective of the CTA is to assess the safety and efficacy of an investigational medicinal product and, as relevant, safety and performance of the device used in combination with the medicinal product.

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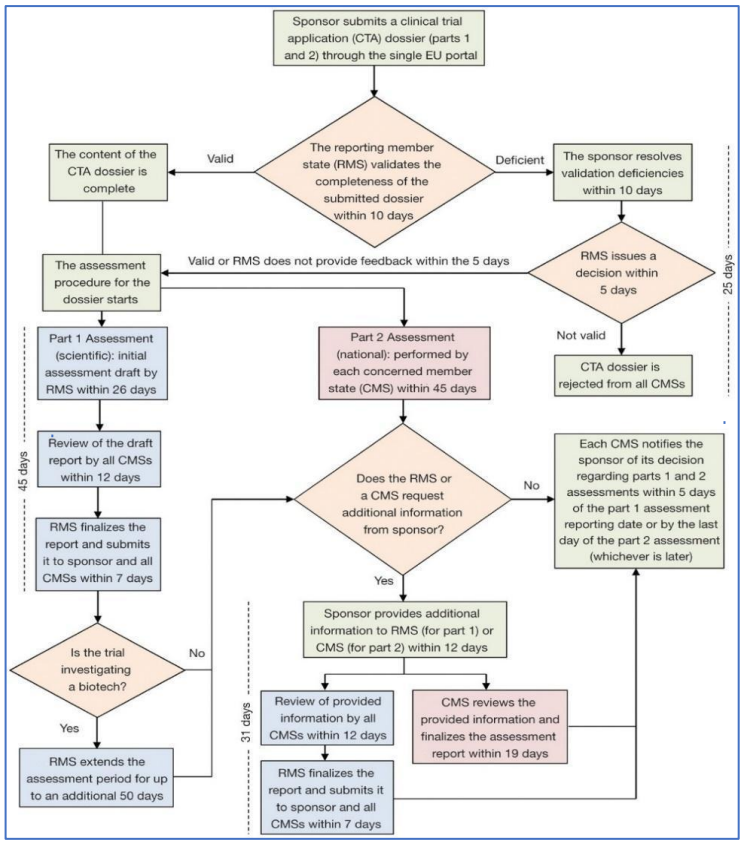
Figure 1 Regulatory pathway for CTAs according to the CTR 536/2014

Part I assessment: Application form, Protocol, IB, GMP documentation, Investigational Medicinal Product Dossier, IMPD (quality, pre-clinical and clinical data related to the potential risks and benefits of the study – normally follows e**CTD format**). RMS coordinates joint review with CMS – total 45 days. Day 55 Part I assessment report with all CMSs in agreement



Part 2 assessment: Country specific – IC, PIL, Compensation arrangements, recruitment, investigator and facility suitability, damage compensation, data

Ref 10: Abou-El-Enein, M., Schneider, C. Deciphering the EU clinical trials regulation. *Nat Biotechnol* 34, 231–233 (2016).

4. BACKGROUND: EFPIA SURVEY RESULTS

In December 2022 EFPIA launched an anonymized survey to gather data from EFPIA Members on EU CTAs with MDs. Fifteen (15) EFPIA members responded in January 2023 and a summary of the most relevant points of the survey for this position paper are provided below.

Types of devices of most interest:

- Integral 93% (14 members)
- Co-packaged 73% (11 members)
- Standalone devices used in the clinical trial with medical purpose 67% (10 members), which may include software device (MDSW)
- Separate from medicinal product, i.e., standalone devices referenced in the IMP handling manual 53% (8 members)

Seven key hurdles for CTAs were presented to the participants and ranked (see Table 1 below). Clearly, the largest percentage of challenges encountered (75%) lies in the lack of consistent documentation requirements across Member States for MDs. Inconsistent interpretation by National Competent authorities of the Member

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States of which MDs used in medicinal products trials require application under the EU MDR is the second most common challenge faced by the Sponsors (63%) due to non-harmonized approach and requirements when implementing provisions of Art. 62 and Art 82.

Table 1 – Most common types of challenges for CTAs with MDs

What are the key hurdles you are facing?	% (*)
H1. CIA documentation not consistent across MS	75
H2. CIA submission process not consistent across MS	63
H3. Timing of Ethics Committees reviews is not consistent and poses challenges for planning	63
H4. Inconsistent interpretation of which trials require applications under the EU MDR	63
H5. MS have inconsistent positions regarding the timing of applications relative the CTA under the CTR	50
H6. CIA documentation expectations are too burdensome	38
H7. Review of CIA is not meeting MDR timelines	25

(*) Percentage of the number of clinical trials facing the hurdle.

Inconsistent interpretation of which trials require applications under the EU MDR at the interface of CTR (H4), and documentation not consistent across MS (H1) are addressed in this reflection paper.

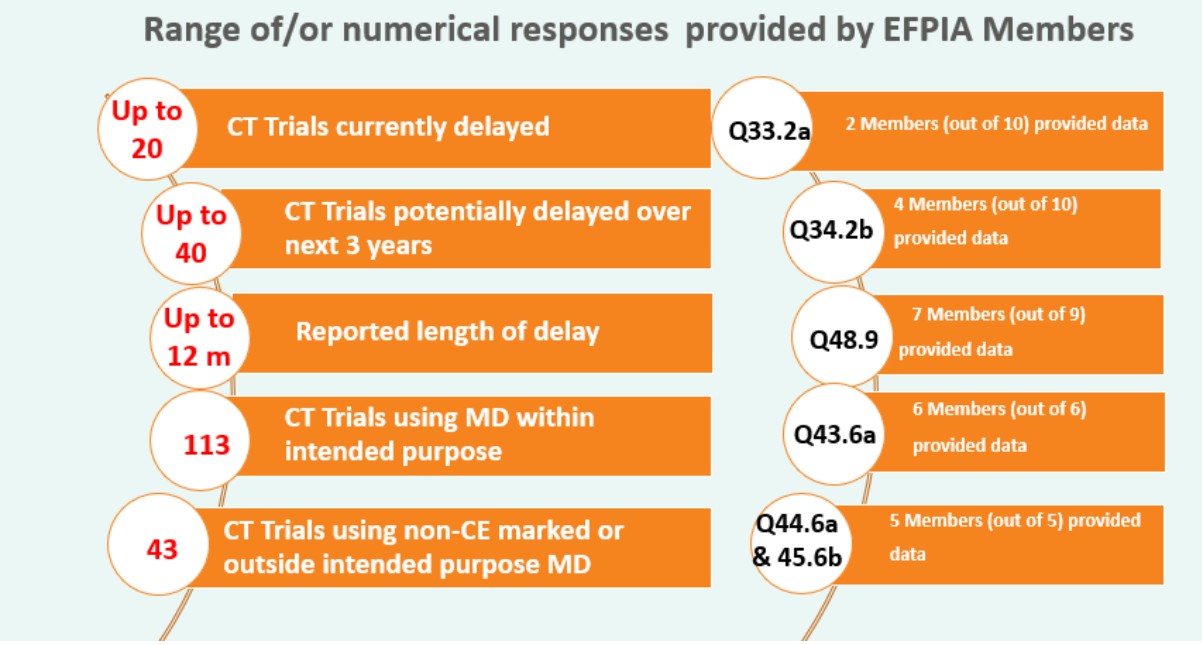
Given the evolving landscape of combined medicinal product and MD applications (CTA & CIA) with Member States still developing processes, requirements, requests for additional information, and review procedures, EFPIA members supplied feedback on:

- the number of trials affected by delays,
- the estimated duration of these delays
- the number of trials involving MDs categorized as CE marked within their intended purpose, used outside their intended purpose, and non-CE marked.

Please see below regarding the relevant questions asked as well as a summary of the corresponding responses to the EFPIA survey and the following questions:

- Q5.2: Do you perform clinical trials with: (Please select all that apply)
- Q33.2a. Number of these CT being currently delayed due to MDR requirements?
- Q34.2b. What is the number of these clinical trials in the EU that may be delayed due to the MDR requirements?
- Q48. 9. Potential length of delay for these clinical trials on average?
- Q43. 6a(i). How many clinical trials will use CE Mark device within its intended purpose?
- Q44. 6a(ii). How many clinical trials will use CE Mark device outside its intended purpose?
- Q45. 6b. How many clinical trials will use non-CE Mark devices?

Figure 2 EFPIA survey January 2023 - IMP clinical trial study with MDs



5. CONSIDERATION FOR REGULATORY PATHWAY FOR CTA USING MD: DECISION TREE PROPOSAL

As part of the transition from MDD to MDR, manufacturers face challenges regarding CE-marked devices that may see their intended purpose restricted, unless additional clinical data are provided to support the prior intended purpose under MDD. This may result in a change of a device used within its intended use (under MDD) to a device used outside of the intended use (under MDR).

In the absence of CE marking for its intended purpose, the generation of evidence that the MD meets the relevant GSPRs for the specific purpose of the clinical trial should be done by the CTA Sponsor with the manufacturer of the device to ensure safe and effective use of the device in the clinical trial.

The CTA Sponsor should conduct a risk-benefit assessment if a CE-marked device is used outside its intended purpose and/or if a non-CE-marked device is used in a clinical trial. The manufacturer of the device should be consulted to gain insight into the residual risk of the MD.

From a regulatory submission perspective, both EMA/CHMP QWP & BWP guidelines (Ref 5) on the requirements for quality documentation concerning chemical and pharmaceutical (QWP) or biological (BWP) investigational medicinal products in clinical trials have the following requirements in section P.7 Container Closure System:

"If a MD is to be used for administration its regulatory status should be explicitly stated (e.g. whether it is CE marked for its intended purpose or not). In the absence of certification for its intended purpose, a statement of

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compliance of the MD with relevant legal requirements for safety and performance is required". EFPIA proposes that the following decision tree could be used in a risk-based approach to define the documentation requirements for a CTA. In the opinion of the EFPIA MQEG, this proposal complies with Annex III and complements Annex I of MDCG 2021-6 Questions & Answers regarding clinical investigation (Ref 8).

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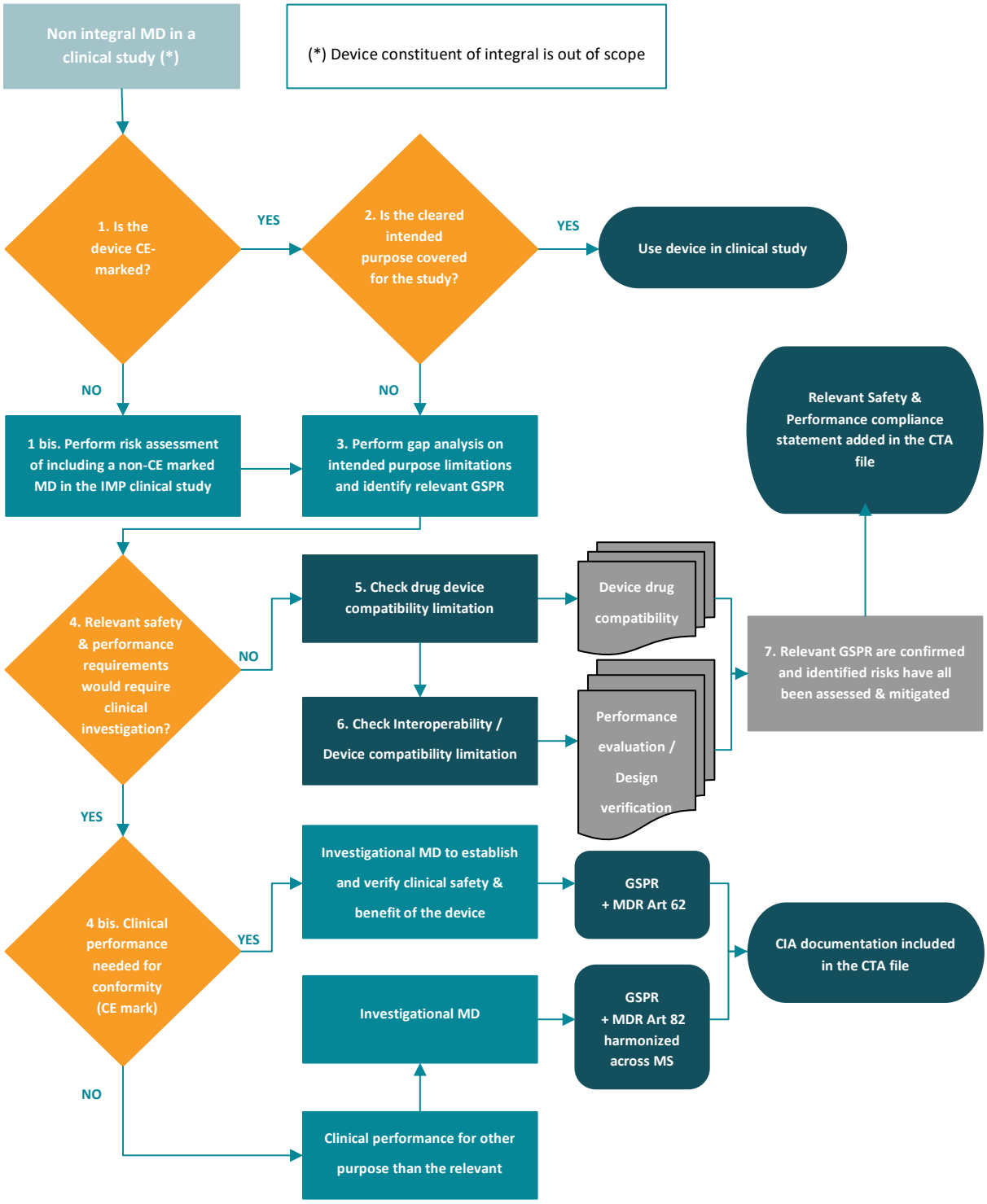
Figure 3 - Proposed Decision Tree for risk-based approach supporting compliance statement with relevant requirements for safety and performance.



EFPIA considers this approach to be adequate based on the following considerations:

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1. The scientific and quality information required to support the device's use in the clinical trial - to demonstrate that it is fit for purpose from a safety and performance perspective - are provided by the Sponsor in partnership with the manufacturer of the MD. An adequate and approved quality agreement outlining this relationship between these two actors is essential.
2. The pragmatic, risk-based approach already taken by some EU national competent authorities, as illustrated in the case studies 2, 3 and 5 (see Appendix) of this reflection paper. Since the current regulatory perspective is subjective and open to different interpretations, such an approach ensures that the medicinal product and device aspects can be assessed in a coordinated and lean manner without duplication of procedures, when appropriate, i.e., when the CTA goal is the investigation of the medicinal product only.
3. In addition, in the event that a CIA under MDR would be required, EFPIA advocates for clarification about the applicability of MDR Article 62 vs Article 82, and an EU harmonization of the member states requirements for Article 82 (Ref 11. Podhaisky H.-P., April 2024)

Five case studies are presented in the Appendix of the paper with the purpose of illustrating the risk-based approach utilizing the decision tree. Although these case studies are provided by EFPIA member companies that successfully utilized the approach with NCAs within the EU, details regarding the company, medicinal product and also to some extent the MD are not provided for confidentiality reasons.

6. EFPIA PROPOSAL WITH REGARDS TO AN EU CTR & MDR HARMONIZED INTERPRETATION

First, the close interplay between demonstrating the benefit/risk for the medicinal product and the safe and effective use of the MD or the MD software make it highly desirable that the evidence for application for use in a clinical study is provided in one (complete) application. Therefore, sufficient expertise within the Health Authorities for their review is highly desirable and needed to ensure such integrated review pathways, i.e., a concurrent review and assessment of device documentation of compliance to safety and performance requirements together with the CTA documentation.

Furthermore, to ensure a consistent interpretation across all competent authorities of the CTR at the interface of the MDR, the following proposed solutions would help to clarify and streamline the submission and the subsequent review process:

- Add clarity regarding the definition of a MD with the sole purpose of delivering a medicinal product (i.e. the generation of clinical data on the device is not an objective) or MDSW that serves a specific medical purpose as part of a clinical trial, and supplement this with the specific MDR requirements that are required to provide evidence of safe use of these in clinical studies.

- The recently updated Clinical Trials Regulation (EU) N° 536/2014 Questions & Answers Version 6.9 (Ref 4) describes this type of administration device under Question 1.12 -Paragraph 43b, i.e. *"the MDs not being object of the study have to comply with the EU-rules for the placing on the market and putting*

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into service of MDs". This would address both the need for protecting the patient by demonstrating EU MDR Annex I compliance for the specific intended purpose whilst avoiding duplication of information and unnecessary regulatory burden imposed by a CIA submission.

- A clarification regarding the requirements and/or the risk-based approach for demonstrating compliance to safety and performance for MDs (non-CE marked or CE marked and used outside of its intended purpose) not subject of the clinical study.

- Issue a procedural provision, or an overarching guideline that would address a harmonized interpretation of the EMA guidelines. Specifically:

  1) Definition and clarification of the regulatory pathway, when devices are used in the clinical trial outside their intended purpose and no device related endpoints will be assessed.

  2) How the responsible party(ies) using the MD in the clinical trial would provide evidence that the MD is fit-for-purpose.

  Since the EMA/CHMP guidelines (Ref 5) introduced the wording 'Compliance statement', it would be appropriate to ensure an aligned wording/definition between EMA/CHMP and MDCG guidelines and/or MDR regulation.

- Leverage the "All-in-One-Project" from the ongoing COMBINE program of the EC by considering having clinical trials with "combined use" of medicinal product and MD with a coordinated review from both competent authorities and ethics Committees.

- Finally, ensure a harmonized interpretation across the EU member states regarding the use of MDR Articles 62 and 82 including a clarification that MDR Article 82 may be applied to investigational devices used in medicinal product clinical studies where the clinical study does not require device specific safety and performance endpoints. Especially MDR Art 82 section 2 states that '*each Member State shall define any additional requirements for such investigations, as appropriate for each Member State concerned'.* Since commercial clinical trials are most frequently performed in trial centers across multiple EU countries, harmonization of the requirements is of prime importance to support innovation in Europe. EFPIA therefore advocates for the provision of a new MDCG guidance governing such requirements; in the same way that MDCG 2021-6 has been a positive step towards harmonization of clinical investigation requirements.

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Fangjun Zhu, Bayer AG
Hans-Peter Podhaisky, Bayer AG
Louise Place, GSK
Laura Pastor-Sanz, Novo Nordisk A/S
Amanda Matthews, Pfizer

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- Ref 1: "COMBINE" Project (https://health.ec.europa.eu/medical-devices-topics-interest/combined-studies_en#the-combine-project)
- Ref 2: EU MD Regulation (MDR) 745/2017;
- Ref 3: Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use (CTR), and repealing Directive 2001/20/EC;
- Ref 4: Clinical Trials Regulation (EU) N° 536/2014 Questions & Answers Version 6.9;
- Ref 5: EMA/CHMP Guidelines on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, reference EMA/CHMP/BWP/534898/2008 Rev. 2 - Committee for Medicinal Products for Human Use (CHMP) – 27 January 2022. (Note: A similar guideline covers requirements on the chemical and pharmaceutical quality documentation of investigational medicinal products in clinical trials, reference EMA/CHMP/QWP/545525/2017 Rev.2 - Committee for Medicinal Products for Human Use (CHMP) – 27 January 2022);
- Ref 6: EMA/CHMP/QWP/BWP/259165/2019 - Guideline on quality documentation for medicinal products when used with a MD;
- Ref 7: ICH Q8 (R2) Quality Guideline for Pharmaceutical Development;
- Ref 8: MDCG 2021-6 Questions & Answers regarding clinical investigation;
- Ref 9: MDCG 2019-11 Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR;
- Ref 10: Abou-El-Enein, M., Schneider, C. Deciphering the EU clinical trials regulation. *Nat Biotechnol* **34**, 231–233 (2016);
- Ref 11: Podhaisky H.-P., Digital Health Technology in European Clinical Trials, How to Improve the Status-Quo of the Regulatory Landscape? Ther Innov Regul Sci. 2024 Jul;58(4):610-613. doi: 10.1007/s43441-024-00657-y. Epub 2024 Apr 24. PMID: 38656468.EU Clinical Trial Regulation CTR 536/2014.

9. APPENDIX

9.1. Case study based on monodose dry powder inhaler

Background

For inhalation products, a single dose, reusable dry powder inhaler device is commonly used in clinics, particularly in early clinical studies before an associated device is developed. The inhalation powder is contained within a capsule. The inhaler is not the final marketed commercial delivery system, which will be developed at a later stage.

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Considerations needed to develop the risk-based approach for compliance

The delivery system is not the subject of the clinical trial and there are no device endpoint objectives.

The delivery system will not be placed on the market.

There is a quality agreement in place with the manufacturer for clinical use of the delivery system based on data to generate for each clinical use.

Application of the Decision Tree (Decision Tree points 1 & 2)

The delivery system certified intended use does not cover the specific clinical use with the medicinal product and the Sponsor has no intent to commercialize it. The combination Investigational medicinal product/Inhaler is not handled or defined as a single integral product.

1 - The inhaler MD is CE-marked for inhalation of powder products for use within adult patient populations. Investigational drugs are not specifically excluded.

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2 - Is the inhaler used within or outside of its intended purpose? The cleared intended purpose does not cover the use in the intended clinical study, which is for an adolescent population. The CE mark intended purpose of the related delivery system device has been assessed for this clinical trial application by the following characteristics:

- The medicinal product, the therapeutic area and the patient population are novel. Consideration for HCP vs patient, adult vs pediatric, and environment (Supervised vs at home) should be taken.
- The device functionality, mode of action, and the route of administration are unlikely to change (inhalation).
- Depending on the purpose of the clinical trial (e.g. the condition to be treated), the risk classification of the delivery system may change (see also MDR Annex VIII, Rule 20).

Quality, technical, and scientific evidence required to address gaps on intended purpose limitations (Decision Tree Nb 3, 4, 5, 6 & 7)

The manufacturer of the CE-marked delivery system owns the design.

The Quality Target Product Profile (Ref 7), a prospective summary of the quality characteristics of the medicinal product, has been used to select the delivery system and to demonstrate that the delivery system is suitable for the purpose of the clinical trial, i.e., that the medicinal product can be formulated into an appropriately sized capsule for delivery via the delivery system (compatibility) and a safe dose can be delivered to each participant (dose accuracy verified).

Risk assessment for the use of the delivery system with the medicinal product in the specific clinical trial has been conducted and relevant testing has been conducted to support this. It is likely that the GSPRs can be used to help guide the required information, but they should be considered only within the scope of the clinical study.

- The delivery system is safe to use within the constraints of the clinical study. There is no need to generate investigation data for the purpose to demonstrate MD safety and performance within the specific intended purpose of the clinical study.
- The delivery system meets the performance requirements necessary for the clinical study.
- Device components and medicinal product are compatible within the constraints of the clinical study.
- Materials in contact with the medicinal product are safe for use within the constraints of the clinical study (including evidence leveraged from the existing CE marking).
- Materials in contact with the user are biocompatible within the constraints of the clinical study (including evidence leverages from the existing CE marking). Additional consideration has been given to the novel patient population.

Regulatory and procedural perspectives

In the absence of certification for its intended purpose, and based on the above-mentioned evidence, a detailed statement of compliance of the MD with relevant legal requirements for safety and performance is provided by the Sponsor (with input from the manufacturer).

The data supporting the suitability of the delivery system is provided as part of the clinical trial application documentation in compliance with EMA guideline, section P.7 (*). There is no separate MD clinical investigation application required/made.

The device is labelled “For investigational use only”.

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Conclusion:

The close interplay between demonstration of benefit/risk for the medicinal product, safe and effective use for the delivery device make it highly desirable that the documentation is kept in one complete CTA application.

(*) EMA/CHMP/BWP/545525/2017 Rev. 2 - Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials – 27 January 2022.

9.2. Case study based on administration of a novel medicinal product with Class III MD

Background

A CE-marked class III MD is planned to be used in a clinical trial with a novel medicinal product. The CE-marked class III MD is approved for a certain drug that is not the medicinal product IMP studied by the Sponsor, and will be tested prior to its use in the clinical trial to bridge the General Safety and Performance Requirements (GSPRs) to the requirements of the IMP studied in the clinical trial by the Sponsor.

The CE Marking for the device is managed by the MD manufacturer (not the sponsor of the study), under the MD Directive (93/42/EC) (MDD). Transition to MDR (Regulation (EU) 2017/745) is in progress with the manufacturer. The MD might become the delivery system for the commercial medicinal product to receive marketing authorization at a later stage.

Considerations needed to develop the risk-based approach for compliance

The device is referenced by the medicinal product protocol for its administration at the IMP study site. It is provided centrally by the IMP study sponsor.

The clinical study aims at generating clinical data for the medicinal product using the device as a delivery system.

There is a contractual agreement in place with the device manufacturer (quality, safety, full compliance with MDD and agreement that no significant changes will be done that would invalidate the legacy CE mark under MDD).

Application of the Decision Tree (Decision Tree points 1 & 2)

The device is intended to be used by the CTA Sponsor for the delivery of investigational medicinal product. The drug device combination is not a single integral DDC product.

1- The MD is CE-marked under MDD.

2- Is the device used within or outside of its intended purpose? The intended purpose cleared by the CE mark does not cover the IMP and the indication of the intended clinical trial. The CE mark intended purpose has been assessed for this clinical trial application by the following characteristics:

- The medicinal product, the therapeutic area and the patient population are novel.
- The device risk classification (Class III), the device functionality and the route of administration remain the same.

Quality, technical, and scientific evidence required to address gaps on intended purpose limitations (Decision Tree Nb 3, 4, 5, 6 & 7)

The suitability of the device and the compatibility with the medicinal product are checked and traceable to regulatory requirements such as MDR Annex I.

The in-use stability is checked as part of the compatibility study.

The MD set-up provides adequate accuracy of the delivered volume.

Clinical data, generated by the manufacturer with the device used with other medicinal products, are made available to the Sponsor of the clinical study. There is no need to generate investigation data for the purpose to demonstrate MD safety and performance within the specific intended purpose of the clinical study.

Regulatory and procedural perspectives:

A Clinical Trial Application (CTA) was submitted to two countries, country 1 in EU, country 2 outside EU.

Country	Feedback
Country 1	Mixed application in CTA only, no need for separate clinical investigation application. There is a parallel assessment of the therapy and of the MD CMC quality data by both agency divisions for medicines and MD. The device is labelled “for investigational use only”.
Country 2	The device is considered used within its approved intended use, no need for clinical investigation application. The authority explicitly mentioned that the device is CE marked and used in the study within its approved intended use. The device is labelled “for investigational use only”.

Conclusion:

The scientific information required to support the device's use in the clinical trial aims at demonstrating its fitness for purpose from a safety and performance perspective.

The regulatory perspective is subject for interpretation. However, national competent authorities for countries 1 and 2 took the approach to ensure the medicinal product and devices aspects can be assessed in a coordinated and lean manner (no duplication of procedures). The NCA in each of these two countries was competent for both medicinal product and MD. Sufficient expertise with the Health Authorities for their review to ensure integrated review pathways, i.e., a single review procedure and assessment of device documentation of compliance to safety and performance requirements together with the CTA documentation, is highly desirable.

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9.3. Case study based on an ophthalmic syringe

Background

Ophthalmic devices have more stringent requirements to meet than non-ophthalmic devices e.g. external surface sterilization, lower endotoxin limit (2.15 EU/device vs 20 EU/device). In case of siliconized needles or syringes there is the possibility to inject protein-silicon aggregates if there is an excessive amount of residual silicon leading to the formation of "floaters" in the vitreous. Furthermore, there is the possibility to induce a "sterile" inflammation in the anterior or posterior chamber.

In the clinical development phase for ophthalmic medicinal product (vial) general recommendations are made regarding the use of syringes and needles for e.g. intravitreal injections.

A limited number of needles and no syringes are cleared for ophthalmic use, and most are approved for subcutaneous administration (hypodermic needle or general plastic or glass syringe). Some suppliers have even issued Field Safety Notices that their devices are not verified for ophthalmic use.

Considerations needed to develop the risk-based approach for compliance

The delivery system, an empty syringe with a standard Luer-Lock connection, is not the subject of the clinical trial and there are no device endpoint objectives, i.e., no clinical study objectives to assess the performance nor the safety of the device.

The delivery system will not be placed on the market.

The needle is already cleared as a hypodermic injection needle.

Application of the Decision Tree (Decision Tree points Nb 1 & 2)

The combination Investigational medicinal product/Syringe with needle is not an iDDC.

The delivery system is CE marked.
The syringe with a needle MD is used outside of its intended purpose.

Since the syringe and needle are used outside of their intended purpose, the CE mark purpose has been assessed for this clinical trial application:

- The medicinal product, the therapeutic area, the route of administration and the patient population are novel.
- The device risk classification remains the same, i.e. class IIa.

Quality, technical, and scientific evidence required to address gaps on intended purpose limitations (Decision Tree points Nb 3, 4, 5, 6 & 7)

The fitness for purpose of the device was checked based on:

1. Medicinal product-device compatibility studies.

2. Medicinal product-device performance for the intended clinical medicinal product study.
3. Appropriate IFU based on Use Related Risk Analysis (URRA), including warnings in the Investigator's Brochure (IB)
4. Overall benefit-risk assessment reflecting the more stringent requirements for ophthalmic devices (e.g. external sterilization, particles, silicon residues and lower endotoxin limits)

Regulatory and procedural perspectives

Clinical trial applications (CTAs) were performed under Clinical Trial Directive (CTD) and Clinical Trial Regulation (CTR) without any clinical investigation application (CIA).

During CTD Voluntary Harmonized Procedure (VHP), no health authority had asked for a separate device CIA (6 countries EU, 10 countries outside EU).

Conclusion:

Since the CE-marked syringe and needle were used outside of their intended purpose, their use was addressed and justified within the risk management process and appropriate information was provided to the investigators conducting the clinical trial.

The national competent authorities took an approach to ensure the medicinal product and devices aspects can be assessed in a coordinated and lean manner, i.e., with no duplication of application procedures.

9.4. Case study based on Digital Health Technology (DHT) that qualifies as MD Software (MDSW) with ophthalmological indication

Background

A non-CE marked MDSW with ophthalmological indication to visualize and quantify retinal fluid is used in a multinational European medicinal product trial without being the objective of this study but to monitor the therapy with the pharmaceutical product.

The sponsor of the medicinal product trial is not the same as the manufacturer of the device under development and both companies partner for the project.

The combined use of the medicinal product and the MDSW will not be marketed together but just used for the purpose to drive the conduct of the medicinal product clinical trial.

Considerations needed to develop the risk-based approach for compliance

The MDSW is a non-invasive device that is intended to assess the efficacy and the pharmacodynamic of the pharmaceutical product as an exploratory endpoint in a medicinal product trial. A comprehensive design-control documentation was provided by the manufacturer reflecting the clinical use case in the medicinal product trial. This design control documentation, including all software specific aspects (e.g., cybersecurity), were provided to the competent authorities. In addition, a contractual framework between the manufacturer of the DHT/MDSW and the Sponsor of the medicinal product trial was established including device specific pharmacovigilance aspects.

Application of the Decision Tree (Points Nb 1 to 7)

1 - A non-CE marked MDSW is used in a clinical trial.

1bis - The CTA is supported by comprehensive design control data based on a risk-assessment of the clinical use case.

3 - & 4 - It has been assessed that compliance to relevant GSPR for this clinical study would not need to generate clinical investigation data.

5, 6 & 7 - All relevant GSPR are confirmed, and remaining risks have all been mitigated.

Regulatory and procedural perspectives

Multiple and diverse feedback were received from all competent authorities (CA) and Ethics Committees (EC) involved. While the computer validation and the data supporting compliance to relevant safety and performance requirements were accepted by all stakeholders involved, the feedback concerning the regulatory pathway was not harmonized among the European authorities: Some authorities asked for an additional Article 62 application according to MDR, in parallel with the CTA, others suggested an Article 82 application. One EU member state health competent authority enabled an integrated approach and the inclusion of the design control data for the non-CE marked MDSW into the documents for the CTA as an 'Annex' amendment. An authority located outside the EU suggested a comparable approach of an integrated submission.

Conclusion:

A harmonized interpretation is needed with regards to the applicability of MDR for cases where MDSW are used to drive medicinal product development. EFPIA supports integrated approaches, i.e. inclusion of relevant device documentation as part of the CTA, as already available with some EU & non-EU authorities.

In addition, assuming that a clinical investigation under MDR would be required, EFPIA advocates for clarification about the applicability of MDR Article 62 vs Article 82, and an EU harmonization of the member states requirements for Article 82 (Ref. 11 Podhaisky H.-P., April 2024)

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9.5. Case study based on an automated dose guidance solution (DHT qualifying as MDSW)

Background

Dose guidance solutions are tools or systems designed to provide recommendations and support for medication dosing, especially in the context of conditions such as diabetes or other chronic diseases. They can contribute to better treatment management, improved quality of life for individuals with diabetes, and potentially reduce long-term complications associated with poorly controlled blood sugar levels.

The dose guidance solution of this case study is intended to support the treatment of diabetes by providing dose guidance to the patient. It is intended to be used in home and healthcare facility environments.

The dose guidance solution includes a patient facing application (app), a dose guidance web portal to be used by the Health Care Professional (HCP), and a computer engine for dose guidance calculation.

The HCP defines a treatment plan (starting doses, blood glucose target ranges). The patient provides input (several consecutive fasting blood glucose (FBG) measurement, dose injected and information about hypoglycaemic events. Based on all these parameters, the engine calculates an adjustment to the current doses. The app provides a recommended dose to the patient.

The dose guidance solution was used during a clinical trial for an innovative medicinal product for the treatment of diabetes, in order to investigate the combined effect of the medicinal product used together with the dose guidance solution.

At the time of submission of the Clinical Trial Application (CTA), in early 2021, the MDR was published but not effective. However, the clinical trial was run after the MD Regulation (MDR) became effective (26 May 2021).

Considerations needed to develop the risk-based approach for compliance

The CTA Sponsor is the manufacturer of the dose guidance solution, which was developed & manufactured by a supplier before the MDR 2017/745 became effective. The supplier provided all necessary information to guarantee compliance with the Essential Requirements in the MD Directive (MDD).

The dose guidance solution was not the subject of the clinical trial and there were no device endpoint objectives. However, it played a key role in guiding the dose setting and therefore was part of the disease/ patient management..

The dose guidance solution in this use case did not undergo a conformity assessment process. It was not intended to be placed on the market.

Application of the Decision Tree (Points Nb 1, 1bis, 3, 4 & 4bis)

The combined use of Investigational medicinal product/ MDSW is not an integral DDC product.

1 - The automated dose guidance application is a MDSW, which is a non-CE-marked device.

1bis - The risks of including a non-CE-marked MDSW in the clinical trial were assessed: The MDSW was used within its specific medical purpose and only in the context of the medicinal product clinical trial.

3 - The system was thoroughly validated. The fitness for purpose of the device was checked based on:

- Assessment of performance data of the MDSW solution considering the particular case of the medicinal product trial;
- The software was accompanied by an information for the user (IFU) that was validated prior to its use.

4 - Even though there were no device endpoint objectives, the use of the dose guidance solution had an effect on the clinical endpoint (Hba1c) and clinical investigation was required.

4bis - Clinical data was not needed for conformity assessment. It is the CTA Sponsor quality and regulatory judgment that MDR Article 82 should be followed.

Regulatory and procedural perspectives:

The clinical trial was run both outside and in EU:

- Outside Europe, one country required one CTA file only, including the device documentation, while another country required an investigational testing authorization as a parallel application.
- The Clinical Trial Applications (CTAs) in Europe were submitted under the Clinical Trial Directive (CTD). CTAs were submitted in seven European countries, two of those not being EU MS but following EU legislation. Four countries required a separate medicinal product and device clinical application (CTA and CIA). One country only required a CTA submission. One country allowed the submission of an integrated CTA including the device documentation. One EU MS rejected the CTA, considering that it was not allowed to run a medicinal product clinical trial using a MDSW under development.

Conclusion:

The various national competent authorities (NCA) in EU took different approaches regarding the submission process:

a) Separate applications for medicinal product (CTA) and device (CIA) (4 countries, 3 of those are MS the other one follows EU legislation); b) No need for device CIA (1 country, non MS but following EU legislation); c) integrated CTA including device documentation (1 country, non MS but following EU legislation); d) Rejection of the CTA considering that it was not possible/allowed to run a medicinal product clinical trial including a MDSW (1 MS).

The pragmatic approach of an integrated medicinal product/device documentation (as in c)), i.e., data supporting compliance to the relevant general safety and performance requirements as part of the CTA, would be the preferable option to ensure that the medicinal products and MD software(s) can be assessed in a coordinated and lean manner. This approach, resulting in no duplication of procedure, was supported by one MS in the EU, and supported by one major country outside the EU.

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