CTIS Bitesize Talk: Alternate IMPD-Q and New guidance AxMP

24 April 2024

Event supported by Monique Al (CCMO); Stefan Strasser (AGES); Anne Lenaers (FAHMP); Ana Rodriguez (Data Analytics and Methods Task Force, EMA)

A few housekeeping rules

Questions were collected in advance on **www.sli.do**
With event code **#bt24apr**

Tips for optimal screen viewing

- Make use of the instructions under the **Live broadcast** section on the event page and connect directly to the **EMA's Vimeo channel 1** *for the full-screen experience*
- Have a stable internet connection

Agenda

- Recommendations on the use of Auxiliary Medicinal Products (AxMP) in Clinical Trial
- IMPD-Q
- Q&A session

The experts for this events are:

Moderator: Roxana Spulber

Ana Rodriguez

CTIS Product Owner, EMA

Stefan Strasser

Clinical Trials Department, Austrian Medicines and Medical Devices Agency

Monique Al

Special Advisor CCMO, Vice-chair CTCG, co-chair MedEthicsEU

Anne Lenaers

Regulatory Expert at the Belgian National Competent Authority

Recommendations on the use of Auxiliary Medicinal Products (AxMP) in Clinical Trial

Presented by Monique Al, Special Advisor CCMO, Vice-chair CTCG, co-chair MedEthicsEU

Centrale Commissie Mensgebonden Onderzoek

ccmo

Recommendations on the use of Auxiliary Medicinal Products (AxMP) in Clinical Trial

RECOMMENDATION PAPER ON AxMPs IN CLINICAL TRIALS
endorsed by CTAG
version 1 March 2024, Published on Eudralex Vol. 10

Auxiliary Medicinal Product

Definition AxMP - CTR, Article 2 (8)

“A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product”.

Preamble 54, CTR

*“..... distinction should be made between investigational medicinal products ..... and auxiliary medicinal products ....., such as medicinal products used for ..... in a clinical trial. **Auxiliary medicinal products should not include concomitant medication**s, that is medications unrelated to the clinical trial and not relevant for the design of the clinical trial.*

A medicinal product relevant for design clinical trial

Not an investigational medicinal product

Not concomitant medications

Investigational medicinal product (IMP)

Definition IMP - CTR, Article 2 (5)

“A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial”.

A medicinal product

Test product, Reference product (comparator), Placebo

Examples AxMPs (annex I of the recommendation paper)

- rescue medication (“escape medication”)
- challenge agents
- to assess endpoints
- background treatment.

Authorised diluents, such as saline, are not considered an AxMP if combined with IMP prior to administration. They are then regarded as excipients in the finished IMP.

Background treatment: AxMP or IMP?

Background treatment:

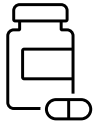
- This type of medicinal product is administered to each of the clinical trial participants, regardless of randomisation group:
  - to treat the indication which is the object of the study or
  - required in the protocol as part of standard care for a condition which is not the indication under investigation and is relevant for the clinical trial design.
- Background treatment is generally considered to be the current standard of care or part thereof for the particular indication.

- Background treatment should be described in protocol
- If specific treatment regimen for standard of care is mandated in the protocol, it should be clearly specified by active substance, ATC code (level 3-5) or drug product.
- If there are discrepancies between MSs in clinical practice between MSs, a justification should be provided in protocol and potential bias should be addressed.

Background treatment: AxMP or IMP?


IMP-X


SoC A


Placebo

Active group	Control group	Objectives of clinical trial	IMP	AxMP
		To study the efficacy and safety of a new IMP-X in patients on continued SoC-A treatment (IMP-X compared to placebo)		
		To study the efficacy and safety of a new IMP-X in patients on continued SoC-A treatment (IMP-X compared to SoC-A)		
		To study the efficacy and safety of IMP-X in combination with SoC product in patients with disease Y.		

Requirements AxMP

- In principle, only authorised medicinal products (in EU/EEA)
- Use of unauthorised medicinal products to be justified:
  - no authorised auxiliary medicinal product available in EU/EEA or
  - the sponsor cannot reasonably be expected to use an authorised auxiliary medicinal product (e.g. magistral or official formula)
- free of charge for the trial participant, unless the law of the MS provide otherwise

Authorised medicinal products are medicinal products authorised in any Member State concerned in EU/EEA , irrespective of changes to the labelling of the medicinal product.

Documentation AxMP

Unauthorised AxMPs and authorised AxMPs which are modified*

- Similar requirements as for IMP (CTR annex I section F (GMP) and G (AxMPD) for initial application and annex II for substantial modification)
- Description of the content of the labeling
- Reference safety information (RSI) – clearly identified section in IB/SmPC
- Product has to be registered as structured field in CTIS
- Unauthorised AxMPs have to be registered in the eXtended EudraVigilance Medicinal Product Dictionary (XEVMPD) database before they can be added in CTIS.

Authorised unmodified AxMPs

- AxMPs should be listed in cover letter (Active substance, ATC code (level 3-5) or drug product)
- *No SmPC has to be submitted*

* Modifications which are not covered by the marketing authorization and affect the product quality and/or GMP requirements

Safety reporting AxMPs

Unauthorised AxMPs and authorised AxMPs which are modified*

- Safety reporting similar requirements as for IMP
  - Investigators/sponsors to collect, record, manage and report of adverse events/reactions as described in article 41 and 42 of CTR
  - SUSARs to be reported to Eudravigilance
  - All serious adverse reactions (SARs) to be included as line-listing in Annual Safety Report (ASR) of the respective IMPs
  - Any safety issue to be included in ASR as well
  - No separate ASR is needed

Authorised unmodified AxMPs

- Safety reporting in relation to the authorised AxMPs should be done in accordance with Pharmacovigilance rules provided in Chapter 3 of TITLE IX of Directive 2001/83/EC (art 46 CTR)
- Investigator/sponsor are encouraged to also report adverse reactions to the competent authority of MS where the reaction occurred OR to the marketing authorization holder of the AxMP.

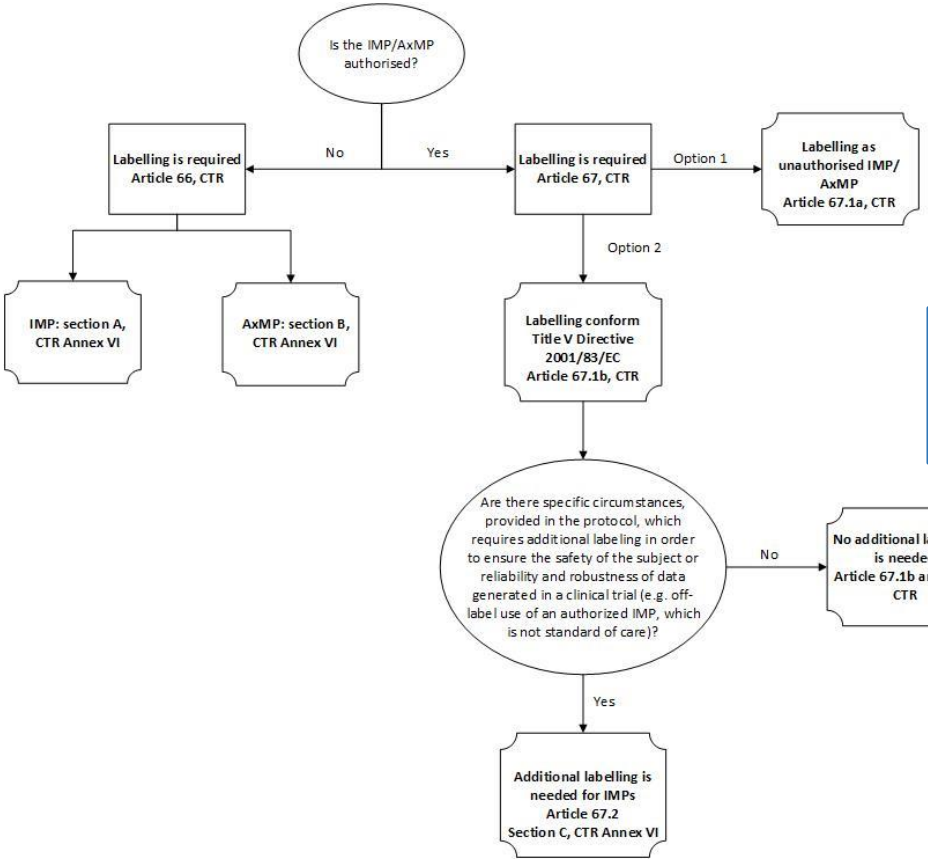
See also chapter 7 of COM Q&A on CTR on Eudralex volume 10.

* Modifications which are not covered by the marketing authorization and affect the product quality and/or GMP requirements

Serious breaches, Unexpected events and Urgent Safety Measures

- Reporting requirements described in article 53, 53 and 54 of CTR
- Also applicable for AxMP (authorised and not authorised)

Labeling AxMP (annex 2 of recommendation paper)



Sourcing from different MAHs and/or different MSs in the EU/EEA is allowed provided any language related re-labeling is covered by exemption of article 61.5a of CTR (see further annex V of COM Q&A CTR)

Centrale Commissie Mensgebonden Onderzoek

ccmo

Thank you for your attention!

https://health.ec.europa.eu/document/download/47ad006a-6ad4-488d-bb51-ab91d11e2871_en?filename=2017_06_28_recommendation_on_axmps.pdf

Auxiliary Medicinal Products in Clinical Trials

Recommendations on the use of Auxiliary Medicinal Products in Clinical Trials written and endorsed by the Clinical Trials Coordination and Advisory Group (CTAG)

March 2024

Document history:	
Date of endorsement by CTAG	19 February 2024
Date of publication:	1 March 2024
Supersedes:	Version 28 June 2017
Changes compared to superseded version:	- Minor editorial changes. Section 3.2 on the documentation required for placebos as pre-medication. - Section 3.3 on the documentation required for unmodified authorised AxMP. Annex 1: - Challenge agents: recommendation only applicable for challenge agents that are medicinal products. - Background treatment: update on the classification IMP vs AxMP if medicinal product is standard of care. Addition of annex 2 with flowchart on labeling requirements

Important notice: This document should be read in combination with the Clinical Trials Regulation (EU) No 536/2014. The information and views expressed in this document may not in any circumstances be regarded as stating an official position of the European Commission or its services. Ultimately, only the European Court of Justice can give an authoritative interpretation of Community law. Additional supportive documents can be retrived on Eudralex 10: https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-10_en

IMPD-Q

Presented by Stefan Strasser, Clinical Trials Department, Austrian Medicines and Medical Devices Agency

Bundesamt für Sicherheit im Gesundheitswesen
BASG

IMPD-Q-only FAQ Update 2024

Stefan Strasser, MD

Clinical Trials Department, Austrian Medicines and Medical Devices Agency

Disclaimer

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The content of this presentation reflects the personal knowledge, experience and view of the author.
- It does not necessarily represent the view of the Federal Agency for Safety in Health Care (BASG), the Austrian Agency for Health & Food Safety (AGES), the European Medicines Agency (EMA) or the European Commission (EC).
- Any omission or truncation of regulatory requirements found within this presentation does not relieve any entity or person of their legal obligations to fully comply with all applicable regulatory requirements.

IMPD-Q-only in a nutshell

Let's start with the basics.

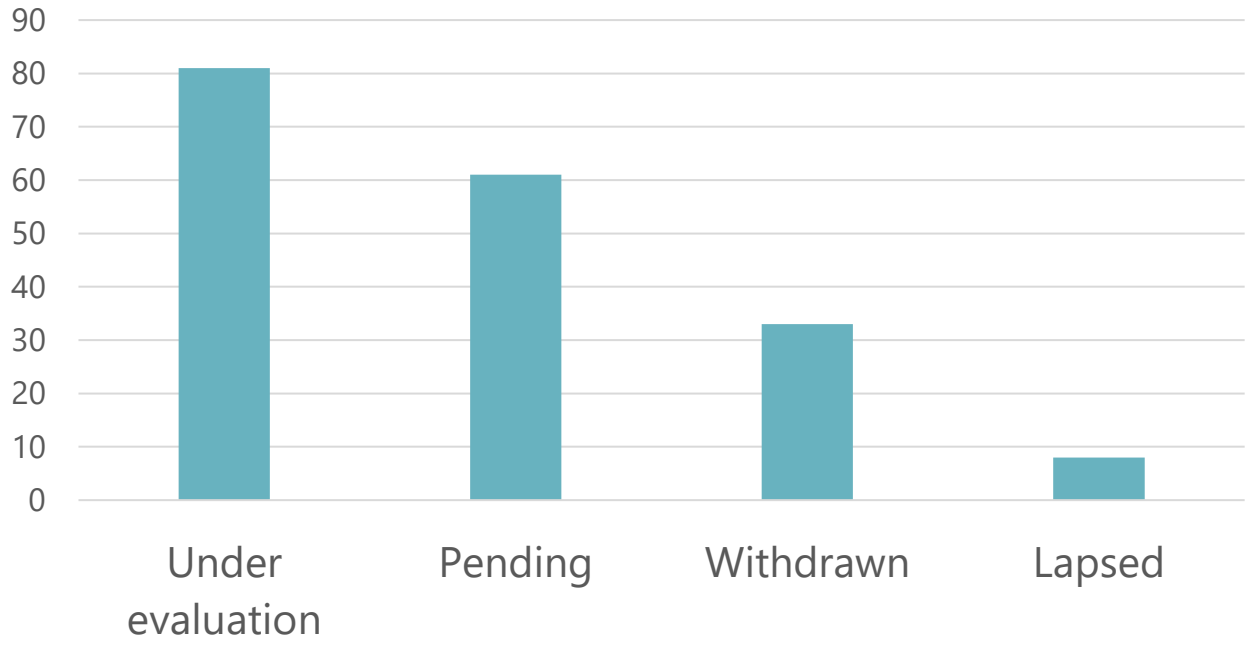
Bundesamt für Sicherheit im Gesundheitswesen
BASG

- Workaround developed to allow **for the product owner (PO) to keep manufacturing information confidential from the sponsor** in a trial they support with an IMP or AMP.
- **Cooperative approach with bilateral responsibility** and additional administrative burden.
- Parallel application via CTIS.
- Parallel workflows allow **considerations/RFI and responses to be separated** between sponsor and PO.
- IMPD-Q-only application is **not approved.**
- IMPD-Q only applications **do not have a life-cycle in CTIS.**
- CTIS functionality would be preferred by all parties.

183 IMPD-only applications so far

CTIS Trial Search 2024-04-22

Bundesamt für Sicherheit im Gesundheitswesen
BASG



Update for association of CTR trials in CTIS

Minor issue (and only a sideline to IMPD-Q-only)

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- In case of a new clinical trial application in CTIS: if the PO is also the sponsor of another clinical trial with the same IMP ongoing under the Regulation, **a cross-reference to the other clinical trial should be made via the function "Associated clinical trials".** The cross-reference should be described in the cover letter, and an explanatory document should be uploaded in the IMPD-Q section.
- If the reference trial is **not ongoing under the Regulation, this trial should first be transitioned** in accordance with the Commission guidance for transition of clinical trials from CTD to CTR before it can be used for cross-reference.
- When the planned trial is **not performed in a similar population, or when e.g. the dose or route of administration is different compared with the ongoing trial with the same IMP**, the parallel submission described under point 129 can be used for considerations to reach the PO directly.

Correction for required documents

Minor issue

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The “IMPD-Q-only application” shall … include the following:
  […]
  - the IMPD-Q and any supporting documents **in accordance with Annex I, section F and G of the Regulation**

- In the “sponsor trial” reference should be made to the “IMPD-Q-only application” in the cover letter, stating the EU-CT number of the “IMPD-Q-only application”. Instead of the IMPD-Q, a Letter of access document should be uploaded referring to the “IMPD-Q-only application”. **Content of the labelling of the IMP in accordance with Annex I, section J of the Regulation should also be uploaded in the “sponsor trial”.**

Clarification for stringency of timelines

Minor issue

Bundesamt für Sicherheit im Gesundheitswesen
BASG

- The PO can submit the IMPD-Q to CTIS via an initial application for Part I only ("IMPD-Q-only application"). The "IMPD-Q-only application" must be submitted at the same time as the initial application of the trial for which the IMP is intended ("sponsor trial"). **It is recommended that both submissions are not more than 24 hours apart.**
- The **same MSCs** should be selected for both applications, and the **same RMS** should be proposed.
- In case of validation considerations in only one of the two applications, a validation consideration will also be raised in the other application to harmonise the timelines of both procedures.
- **It is recommended to address all validation considerations at the same time.**

Ensure sponsor/PO cooperation

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Important!

- **Full cooperation between** PO and trial sponsor is required for this approach.
- **Sufficient information regarding the drug substance/product and IMP information should be shared** with the sponsor by the PO as a basis for the sponsor's risk assessment and responsibility for the clinical trial.
- Any **changes** in the IMPD-Q only that could **impact the safety and/or quality** of the IMP should also be **shared** between the PO and trial sponsor.
- **Contractual agreements** should be in place to define bilateral responsibilities and sharing of information.
- The "IMPD-Q-only application" shall … include the following:

  a statement by the product owner to acknowledge the legal, procedural and technical rules of the Regulation, CTIS and this Q&A and a commitment to fully cooperate with the sponsor to fulfil their legal requirements

SMs and AMs – „withdrawal workaround“ I

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Important!

- In case the IMPD-Q is to be used for another application of the same sponsor trial (subsequent addition of a member state, substantial modification or a resubmission) then the procedure described above needs to be repeated.
- For a substantial modification of the IMPD-Q, the product owner **should withdraw the initial IMPD-Q only application and resubmit the substantially modified documentation to all MSC.**
- This allows the **existing information in the IMPD-Q-only application to be re-used** and **to track the application via the resubmission number** (e.g.-00, -01, -02…). This number can then be referenced in the corresponding application in the “sponsor trial”.

SMs and AMs – „withdrawal workaround“ II

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Important!

- Note that with each substantial modification application or changes performed as a result of an RFI, the sponsor **should highlight the specific changes compared to the earlier submitted version**, i.e. in a track changes document and/or in a table listing changes introduced in each version.
- A substantial modification of the IMPD-Q documentation requires the **parallel submission of an application for substantial modification in the “sponsor trial”.** The sponsor should provide a summary description of IMPD changes, while the detailed summary of changes should be part of the IMPD-Q-only application. An updated list from version to version is considered helpful.
- In the same way **the addition of a subsequent member state to the “sponsor trial” also requires a withdrawal and a resubmission of the “IMPD- Q-only”** application to RMS and the additional MS only, in parallel with the AM application in the “sponsor trial”.

Partial IMPD-Q-only application

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Important!

- The "IMPD-Q-only" application is principally **envisioned to link a full IMPD for one or more IMPs with a clinical trial** in which these IMPs are to be used.
- The scenario that a substance owner (SO) submits the **IMPD-Q for the drug substance (DS) part as "IMPD-Q-only"** and the **drug product (DP) part is submitted in the sponsor trial i**s only possible if the applicable product legislation allows this (e.g. **where a drug substance master file is allowed**).
- A split application is **not allowed for biological medicinal products or ATMPs.**
- Full cooperation between PO and trial sponsor is required for this approach. Contractual agreements should be in place to define bilateral responsibilities and sharing of information (see also point 129).

The Transition Clarification

Bundesamt für Sicherheit im Gesundheitswesen
BASG

Important!

- When a clinical trial is transitioned from the Directive to the Regulation which includes areference to an IMPD not available in CTIS (and where the option described under Point 128 is not feasible), then **an "IMPD-Q-only" submission should be done together with the first substantial modification of Part I after transition**

IMPD, AxMPD,	There is no need to split the IMPD approved in the initial application into separate documents IMPD-Q and IMPD-SE Update IMPD only if the substantial modification concerns *this document*. In line with the revised Recommendations on AxMP/IMPat EudraLex Volume 10[9], in situations when a previous Non Investigational Medicinal Product (NIMP) under CTD is now regarded as an IMP, the	There is no need to split the IMPD approved in the initial application into separate documents IMPD-Q and IMPD-SE Update IMPD only if the substantial modification concerns *this document*. In line with revised the Recommendations at EudraLex Volume 10[9], in situations when a previous Non Investigational Medicinal Product (NIMP) under CTD is now regarded as an IMP, the	-

„No IMPD-Q in CTIS" requires an „update" via IMPD-Q only, even without changes. For future subsequent additons the IMPD-Q needs to be available in CTIS.

Thank you for your attention!

Questions?

Austrian
Federal Office for
Safety in Health Care

BASG

Stefan Strasser, MD

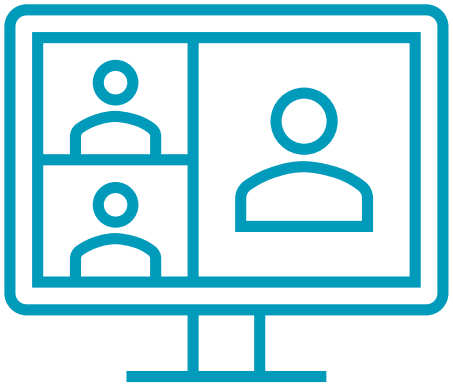
Head of Clinical Trials

BASG -
Austrian Federal Office for Safety in Health Care

Traisengasse 5
1200 Vienna

stefan.strasser@basg.gv.at
www.basg.gv.at

Upcoming CTIS events



- **15 May 2024**, 16:00 – 17:00 CET – CTIS Walk-in Clinic
- **20 June 2024,** 13:30 – 17:00 CET – CTIS Bitesize talk
- For 2024 CTIS events, please consult Clinical Trials Information System: training and support | European Medicines Agency (europa.eu) and EMA events pages

Thank you for attending today's event

Please provide your feedback for this event in our **Slido survey**

Use the passcode: **#bt24apr** or scan the QR code

Further information

For the CTIS Newsletter sign up at https://ec.europa.eu/newsroom/ema/user-subscriptions/3201/create

For upcoming CTIS events visit the EMA event page.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Telephone +31 (0)88 781 6000

Follow us on **@EMA_News**