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Questions and Answers (Q&A) Document

Bitesize Talk on Alternate IMPD-Q and New Guidance AxMP

Disclaimer

This Questions and Answer document is for information only and is based on questions asked during the Alternate IMPD-Q and New Guidance AxMP Bitesize Talk (24th April 2024).

Important notice: The views expressed in this questions and answers (Q&A) document are not legally binding. The European Court of Justice is the only authority that can give an authoritative interpretation of Community law. This document aims at informing on the technical aspects of the Clinical Trials Regulation (EU) No 536/2014 with a view to facilitating its implementation.

For convenience, many technical terms are explained in the table of abbreviations at the beginning of this document.

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Acronym key and glossary terms

ATMP	Advanced Therapy Medicinal Products
AxMP	Auxiliary Medicinal Products
CCI	Commercially Confidential Information
CTCG	Clinical Trial Coordination Group
CTD	Clinical Trial Directive
CTIS	Clinical Trial Information System
CTR	Clinical Trial Regulation
DSMB	Data Safety Monitoring Board
EEA	European Economic Area
EMA	European Medicines Agency
EoT	End of Trial
EU	European Union
FAQs	Frequently Asked Questions
GMP	Good manufacturing practice
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INN	International Non-proprietary Name
LPLV	Last Patient Last Visit
MA	Marketing Authorisation
MS	Member State
MSC	Member State Concerned
MSE	Member State Expert
NSM	Non-substantial modifications
PI	Product Information
PK	Pharmacokinetics
Q&A	Questions & Answers
QP	Qualified person
RSF	Regulatory Support File
RSI	Reference Safety Information
SmPC	Summary of Product Characteristics
SM	Substance Modification

SoC	Standard of Care
xEVMPD	Extended EudraVigilance medicinal product dictionary

1. **Is it required to obtain QP certification for unauthorised AxMPs? If so, is verification against the AxMP dossier and national GMP sufficient, or are there additional expectations (ref. CTR Annex 1) to ensure compliance with standards at least equivalent to EU GMP?**

Yes, QP certification is required for unauthorised AxMPs. The GMP requirements for AxMPs are similar to those for Investigational Medicinal Products (IMPs). If a manufacturer or multiple manufacturers are located in a third country, the QP of the importer must complete and sign a QP declaration, confirming that manufacturing was conducted according to standards at least equivalent to European GMP. Compliance is verified based on the documentation related to product manufacturing, such as batch files, and through audits.

2. **Section 3.1 refers to authorised diluents. Are there also unauthorised diluents, and if so, how should they be managed?**

This question is related to the use of excipients in the finished medicinal product. If an excipient is not authorised, documentation must be provided to ensure the safety and quality of the excipient used in the product. This is fundamentally about patient safety. Thus, if there are unauthorised components in an auxiliary or an investigational medicine, the product will be considered unauthorised, and it will be necessary to provide manufacturing, preclinical, and clinical information to ensure safe use. The primary focus is on achieving patient safety.

3. **If a Reduced Text Label is applied to an authorised AxMP, is it still considered an unmodified authorised AxMP? Does it make a difference whether this activity is performed by a local GMP-compliant vendor or a local pharmacy?**

The label does not affect whether an authorised AxMP is considered unmodified. If the AxMP is unmodified and authorised, the labelling can follow Directive 2001/83, indicating no additional labelling requirements. For the second question, the answer is that it does not matter whether the labelling is done by a local GMP-compliant vendor or a local pharmacy; either is acceptable.

4. **Recent recommendations on AxMPs suggest that a SmPC is not required for authorised unmodified AxMPs. Will this align with Q&A Annex V, which considers authorised AxMPs or authorised IMPs identified by potential trade names?**

It has been recognised that further work is needed in this area. The recommendation paper will be aligned with Annex 5, and this matter will be addressed accordingly.

5. **If an AxMP has obtained a MA through a process other than the centralised procedure and will be administered in a different Member State from the one where it was authorised (e.g., authorised in Italy, administered in Germany), is it necessary to submit the SmPC with a**

translation?

The SmPC does not need to be submitted as part of this clinical trial application. However, it is crucial that the investigator in Germany receives the appropriate product information, especially if the product is only authorised in Italy, as they may not be familiar with it. This is important for safety reasons. In this context, translating the SmPC might be required.

6. **If an authorised IMP is sourced from the EEA, should the language requirements for labelling specified in Annex IV be adhered to, or are there exceptions when dealing with a product with MA instead of an unapproved IMP?**

The language requirements for labelling, even for installations with just one application, are outlined in Annex 2 of the Commission's Q&A and must be followed. There is no distinction between authorised and unauthorised products regarding language requirements.

7. **If a clinical trial protocol has one arm administering IMP with SoC, and another arm administering Placebo with SoC, where the SoC is defined only by drug class and is administered according to its label, would this be considered compliant with the EU CTR?**

A conclusive answer is not possible because it depends on the study's objectives and endpoints, which determine whether the Standard of Care qualifies as an investigational medicinal product. If the SoC is treated as an AxMP, it would be acceptable to specify it by active ingredient, ATC code, or drug product name.

8. **If a sponsor chooses AxMPs from both the local market (by site) and centrally from the EEA, and labels in the local language are required for the central sourcing option, should these AxMPs be included in CTIS?**

Authorised medicinal products are defined as those approved in any member state of the EU or EEA, regardless of any changes to their labelling. Therefore, even if the products are relabelled in local languages, authorised non-modified AxMPs should not be added to the structured data in CTIS.

9. **If an AxMP is sourced centrally from the EEA and relabelled in a local language without any other changes, is it considered unmodified, and does it need to be included in the structured data in CTIS?**

It is still considered an unmodified medicinal product, so there is a no need to include it in the CTIS structured data.

10. **If an authorised unmodified AxMP is not entered into CTIS and the reference SmPC is not uploaded, how can common grounds for assessing safety events be ensured? Is it sufficient to rely on national SmPCs, even if they might vary?**

Safety reporting for an authorised unmodified AxMP should follow Directive 2001/83/EC. There is no requirement for a reference SmPC, and there is no need to rely on national SmPCs.

11. Under CTD, quality information in RSF for vector used in AxMP production of ATMP, was submitted by the PO. Based on the updated response of q2.15 in Q&A, the practice is no longer supported. What should be the approach in these cases?

For biological medicines and AxMPs, the owner and manufacturer of the product must have complete knowledge of the production process. Concealing relevant information is not permitted. If Member States request more information than necessary, it can become problematic, especially in the case of viral vectors, where certain details might not be disclosed without contacting the supplier. This requires careful consideration and further discussions.

12. If a sponsor decides to label authorised AxMPs with a reduced label or in a local language for centrally sourced products, does the label text need to be submitted for approval?

For authorised unmodified AxMPs, label submission is generally not required as part of a clinical trial application.

13. Is it acceptable to provide protocol clarification letter with CTR requirements (EU number, etc) instead of amended protocol at the 1st SM after transition?

No, it is not allowed. During the transition, a low-threshold approach was acceptable, but the updated guidelines now specify the required changes to the protocol for the first substantial modifications. Member States now expect to see a revised protocol at that point.

14. What notifications are required after the transition to the new regulatory framework? Key events to consider for notification include study start and the start of recruitment. However, definitions under the CTR may differ from those under the CTD, affecting when and how to report. What specific dates should be reported?

Under the Clinical Trials Directive (CTD), there was no explicit requirement to notify the study's start date, at least in the directive itself. However, many EU member states, such as the Netherlands, required this notification, though definitions and expectations varied. Given this variability, the advice would be to adhere to the definitions outlined in the Clinical Trials Regulation (CTR), especially for critical dates like the start of recruitment and the first visit by the first patient. If these dates have been recorded, it is important to make sure that they are included when transitioning to CTR. It is possible to add them retrospectively if necessary. If the dates were not recorded, as they were not mandatory under CTD, it is possible to use the date of the first patient enrolled in the study in each member state. This approach aligns with the CTR's requirements while accounting for differences in previous practices across EU countries.

15. Is it possible to report the end of recruitment and the end of the trial with dates that precede the transition approval date?

Yes, once the clinical trial has received an authorisation after being transitioned to CTIS, the sponsor user can report the end of recruitment that precede the transition approval date. However, only clinical trials that have not ended should be transitioned to CTIS. Therefore,. it is not possible to report an end of trial that precedes the transition authoris.ation date

16. Is it acceptable to omit the SmPC for AxMPs listed by INN in the protocol, and instead refer to SmPCs in national databases? This could apply, for instance, to substances that have multiple product names approved at the national level.

For authorised AxMPs and authorised unmodified AxMPs, submitting a Summary of Product Characteristics (SmPC) is not mandatory. However, for other types of AxMPs, you are required to submit the SmPC. If you wish to be considered, you can include a link to the SmPC in a national database within your Clinical Trial Application and Final Agreement (CAFA) letter, but this is not obligatory.

17. Is a sponsor allowed to refer to a previously concluded quality IMPD-only application from a product owner, or is it mandatory to create a new IMPD-Q-only application each time, even though all MSEs have access to all trial applications and related information?

Currently, it is not just about access; it is also about the ability to raise questions, issue a Request for Information (RFI), and receive responses. This functionality is only available if you follow a parallel procedure. Therefore, you must submit a new IMPD-Q for assessment purposes each time.

18. The sponsor views updates to the DSMB (including changes in members and vendors) as non-substantial modifications (NSM). Could you advise if these changes should be considered significant for the clinical trial's supervision and submitted as NSM 81.9?

It should be submitted as a non-substantial modification 81.9. Although it is generally considered a non-substantial modification, the Commission's Q&A on the Clinical Trials Regulation (CTR) in Annex 4, provides various examples of substantial and non-substantial modifications, including 81.9. However, it does not specifically address changes related to the Data Safety Monitoring Board (DSMB). This might be worth adding, especially since changing members could impact the DSMB's independence, which is an important consideration. Nonetheless, it is currently treated as a non-substantial modification under 81.9.

19. Could you advise if the sponsor can request, in the cover letter, the assignment of a specific ethics committee to evaluate the clinical trial? For instance, can the sponsor request the same ethics committee that reviewed a related clinical trial?

The ability to choose a specific ethics committee to evaluate a clinical trial is a national issue and depends on the processes established by individual member states. In many cases, such as in Austria, this would not be possible due to internal algorithms that determine which ethics committee is assigned. Unless there is specific information about national rules, it is likely that in many member states, the choice of ethics committee is not open to sponsors. There may be exceptions, such as in Spain, where sponsors might have some flexibility in selecting an ethics committee, but generally, this decision is made by the National Competent Authority, and for most member states, the answer will likely be no.

20. When creating a substantial modification for part two only, users can currently select just one country. If 10 countries are affected, 10 separate substantial modification submissions are required. Could you clarify if there will be an option in the future to select multiple countries when submitting a substantial modification for part two only?

This feature is not currently in the pipeline. There are other priorities now.

21. Safety reporting for authorised AxMPs must comply with Chapter 3, Title 9 of the Directive 2001/83/EC. What does this mean for a non-commercial sponsor in practice? Does the sponsor need to collect spontaneous safety reports from all sources?

For authorised unmodified AxMPs, standard pharmacovigilance rules apply. Regardless of the classification of the AxMP, it is always the investigator's responsibility to record all adverse events unless the protocol states otherwise. Depending on the type of trial, the collection of safety reports could vary, but this will depend on what is specified in your protocol regarding safety data collection.

22. How should an IMP with an AMM be categorised if it will be used outside its authorised use in a clinical trial? Should it be considered an authorised IMP or an unauthorised IMP?

The product is still classified as an authorised IMP, even if it is being used off-label in the clinical trial. This off-label use should be described in the clinical trial application, but the product itself retains its status as an authorised product, and it should be indicated as such in the structured field.

23. For authorised AxMPs, how can non-commercial sponsors obtain information about potential safety reporting from investigators to marketing authorisation holders or member states?

Safety reporting for authorised unmodified AxMPs adheres to Directive 2001/83/EC, aligning with standard clinical practice regulations. However, it is advisable for sponsors to report adverse reactions to the marketing authorisation holder or the National Competent Authority (NCA) in the jurisdiction where the adverse reaction occurred. Although this is not mandatory, it is encouraged to facilitate proper safety monitoring and regulatory compliance. This approach is confirmed as the expected practice. Investigators collect all serious adverse events and report them, while sponsors must document these events and assess their relatedness to the trial. Additionally, it is recommended that sponsors communicate with the marketing authorisation holder or the NCA in the event of adverse reactions, as mentioned in the guidance. This encouragement implies that it is not obligatory but highly recommended to ensure comprehensive safety reporting.

24. According to the current guidance, AxMPs are authorised and unmodified in accordance with their marketing authorisation, sponsors must declare these in the cover letter. How should sponsors do this? Should they use the product name, ATC classification, or

INN? What is the role of the RSI in this context?

For an authorised unmodified AxMP, the information can be listed in the cover letter, specifying the active substance, ATC code, or drug product name. There is no need to include the reference safety information. In practice, it is best to use the highest level of detail available. For example, if the product is centrally sourced in a member state with favorable pricing and distributed across all concerned sites, you can list it by name. If this is not possible because the product is locally sourced off the shelf, you can identify it by ATC class or INN. When using this approach, it is assumed that the product is nationally authorised, similar to previous practices in EudraCT.

25. For an IMPD-Q application supporting a substantial modification (SM), would all Member States Concerned (MSCs) in the initial application be required, or should MSCs that have received an end-of-trial notification in the sponsored trial be excluded from the IMPD-Q substantial modification application in CTIS?

Submissions are needed only for the Member States Concerned (MSCs), but this must always include the Reporting Member State (RMS), even if an end-of-trial notification has been received. Thus, in the IMPD-Q application, it is crucial to select and propose the same RMS. However, other MSCs that have received an end-of-trial notification do not need to be included, as they would generally be excluded from a substantial modification (SM) application.

26. What is the appropriate approach for a sponsor handling older studies that list all AxMPs? Should the AxMPs be removed from the structured data in Part 1 during the next substantial modification, and instead included in the cover letter, or should they remain in the structured data?

No modifications are required. The AxMPs can remain in the structured data without further alterations. Their current inclusion is appropriate and requires no additional updates with the next substantial modification. It is acceptable to leave them as they are.

27. Is it permissible under the CTR to omit the reference SmPC for locally supplied AxMPs listed by International Non-proprietary Name (INN) in the protocol, and instead refer to SmMPCs in their respective national databases, as was allowed under the CTD?

Submitting the Summary of Product Characteristics (SmPC) is not required for an authorised unmodified Advanced Therapy Medicinal Product (AxMP) as part of a clinical trial application. While it is good practice to reference the national database, it is not compulsory.

28. Is it permissible not to supply or provide IMP/AxMP free of charge in the context of a phase 4 trial that evaluates clinical practices with approved products considered SOC in a real-world

setting?

This is primarily a national matter. The sponsor is generally expected to provide the product, but exceptions may exist, and these are governed by national regulations. In Austria, for example, if a product is considered standard of care, it is possible to apply to the health insurance system to get it covered. However, this approach is strictly national, and checks with the relevant authorities in each member state for specific rules and exceptions need to occur. The regulation does not necessarily oppose this, but it depends on national interpretations.

29. When including AxMPs in Part I structured data, there are often multiple records for the same authorised product. Should all the listings for these products found in CTIS search results be included, or is a smaller selection sufficient?

AxMPs that are authorised and not modified do not have to be included in the structured data in the Clinical Trials Information System (CTIS).