The CMC section of an EU IMPD: Considerations for US sponsors

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Abstract
Sponsors located in the US, developing both chemical and biological investigational medicinal products (IMPs), often perform Phase I studies in the US then conduct Phase II and Phase III studies that include sites located in EU member states. The principal reason is to enable access to a wider clinical trial base. Generally, sponsors use the US investigational new drug application (IND) as a source document when authoring the EU investigational medicinal product dossier (IMPD), either drafting this in house, or contracting this out to a third-party CMC regulatory service provider.

An overriding challenge that is frequently observed in the construction of the IMPD from the IND is that recommendations that are provided in applicable European Medicines Agency (EMA) guidelines, European Pharmacopoeia (Ph Eur) monographs and European Directorate of the Quality of Medicines (EDQM) standard terms database are often not taken in to consideration. As a consequence, non-compliance with EU requirements means that grounds for non acceptance (GNAs) are raised during the review of the clinical trial application (CTA) which sometimes cannot be resolved in time to meet agency response deadlines, resulting in sponsors either having to withdraw a CTA or rejection of a CTA. The aim of this article is to provide guidance on IMPD requirements for US sponsors planning to submit CTAs in EU member states. Potential challenges that can be encountered are outlined.

Introduction

The US FDA and European Medicines Agency (EMA) have both issued detailed guidelines regarding quality requirements for IMPs. Some US sponsors, such as biotechnology companies may be experienced with regard to FDA requirements; however, they may have limited experience with regard to EMA requirements. Furthermore, the sponsor is often under pressure to meet corporate submission milestones to satisfy investors. It is common for sponsors such as small start-up biotechnology companies to take a high-risk approach to the detriment that the IMPD may not be in full accordance with EMA requirements and expectations for the initial CTA submission.

In 2018, revised EMA guidelines on the requirements for quality documentation concerning IMPs containing chemically defined[1] and biological/biotechnology derived[2] drug substances came into effect. Industry stakeholders provided comments regarding the corresponding guidance documents when being revised by the EMA's Quality Working Party (QWP) and Biologics Working Party (BWP), respectively. During the last five years, the EMA has organised workshops focused on quality requirements for medicines containing chemical entities[3] and biopharmaceuticals[4] which included presentations focussed on CMC requirements for IMPs.

Furthermore, there are Ph Eur monographs for some biopharmaceuticals, eg, monoclonal antibodies[5] and gene transfer medicinal products[6] and the EDQM has a standard terms database for pharmaceutical forms[7] that are acceptable in the EU. It is observed that recommendations in EMA guidelines, applicable Ph Eur monographs and the EDQM standard terms database are often not taken into complete consideration when authoring an IMPD. Non-compliance with EU requirements means that grounds for non-acceptance (GNAs) are raised during the review of the CTA which sometimes cannot be resolved in time to meet agency response deadlines. Critically, this can result in sponsors having to withdraw a CTA and sometimes rejection of a CTA due to the inability to provide information to address GNAs. This may lead to delays in site activation and the inability to conduct the study in some EU member states.

The aim of this article is to provide guidance on the requirements for US sponsors preparing an IMPD to include in CTAs that will be submitted to competent authorities in EU member states via the national CTA review process or by the voluntary harmonisation procedure. Due diligence considerations when planning manufacturing of an IMP for evaluation in clinical studies conducted in EU member states and best practice when authoring an IMPD are also discussed.

US IND versus EU CTD requirements

The IMPD sections where information is often not available in the IND source document to address EU requirements, or where an IMPD had been prepared from an IND without taking EU requirements into consideration and submitted to EU competent authorities are highlighted in Table 1 for chemical IMPs and Table 2 for biological IMPs.

Discussion and conclusions

When preparing an IMPD to include in CTAs that will be submitted to competent authorities in EU member states it is important to be aware of applicable EMA guidance documents and Ph Eur monographs to avoid potential GNAs during review of the CTA. From the information

Table 1: Investigational medicinal products that contain chemically defined drug substances.

IMPD section	Applicable extract from EMA Guidance for Chemical IMPs – EMA/CHMP/QWP/545525/2017	Comment and recommendations
Drug substance		
General considerations (Monographs)	For drug substances or IMPs to be used in clinical trials as reference to either the Ph Eur, the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia or the Japanese Pharmacopoeia is acceptable. For active substances, the suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) will have to be demonstrated by the applicant/sponsor. Suitability of monographs of the Ph Eur can be demonstrated with certificates of suitability (CEP) issued by the EDQM. Reference to an Active Substance Master File (ASMF) or CEP is acceptable, If the active substance used is already authorised in a drug product within the EU/EEA or in one of the ICH-regions, reference can be made to the valid marketing authorisation. A statement from Marketing Authorisation Holder (MAH) or drug substance manufacturer should be provided that the active substance has the same quality as in the approved product. Name of the drug product, marketing authorisation number or its equivalent, MAH and the country that granted the marketing authorisation should be given.	US sponsors sometimes provide a full drug substance section in an IMPD even when there is a CEP or ASMF available for the drug substance. It is recommended that sponsors do not follow this approach and if applicable provide a reference to either an acceptable compendial monograph, ASMF, or CEP. If developing an IMP containing a known drug substance and clinical development is planned in EU member states, sponsors should consider using a drug substance that has a CEP. Sponsors can search online for drug substances with CEPs on the EDQM certification database.[8] For an active substance used in a drug product already authorised within the EU/EEA, sponsors should consider making reference to the valid marketing authorisation.
2.1.S.6 Container Closure System	The immediate packaging material used for the drug substance should be stated. If non-compendial materials are used, a description and specifications should be provided.	References to applicable Ph Eur monographs and EU Directives are not provided which results in a comment being included in the GNAs.
2.1.P.1 Description and composition of the investigational medicinal product	Standard terminology from the EDQM standard terms database should be preferably used for dosage forms, where applicable.	Use of a term for a dosage form which is not a standard EDQM term is a common occurrence which results in GNAs being received with regards to the IMPD, EudraCT form and the IMP labelling. Sponsors should proceed with caution here as some competent authorities may ask for the IMP labelling to be corrected, which can cause significant delays to site activation in EU member states.
2.1.P.3.4 Control of critical steps and intermediates	For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable, depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If availability of the formulated medicinal product is limited, a prefiltration/filtration volume of less than 100 ml may be tested if justified. Statement that aseptic processing operations were validated using media fill runs should be provided.	Often in the IMPD, the acceptance criterion for acceptable bioburden prior to filtration is not provided at all or is not aligned with EU requirements. This will be questioned by EU regulatory authorities as they will normally expect an acceptance criterion of NMT 10 CFU/100 mL. For a test volume of less than 100 mL, a justification will need to be provided in the IMPD. With regard to media fill runs, often a sponsor is asked to provide a summary of the results to demonstrate the efficacy of the aseptic processing operations.
2.1.P.7 Container Closure System	The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph.	References to applicable Ph Eur monographs and EU Directives are often not provided, which results in a comment being included in the GNAs.
2.1.P.8 Stability	For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (eg, appearance, assay, impurities, visible and sub-visible particles, microbial contamination). Shelf life and storage conditions after first opening and/or after reconstitution and/or dilution should be defined. These studies are not required if the preparation is to be used immediately after opening or reconstitution and if it can be justified that no negative influence on the quality of the preparation through instabilities is to be expected.	In use stability data is often not provided, even in cases where the reconstituted or diluted IMP is stored for many hours before being administered to a study subject. It is recommended to provide in-use stability data in the IMPD.
Appendices		
2.1.A.4 Solvents for reconstitution and diluents	For solvents for reconstitution and diluents, the relevant information as indicated in section 3.2.P of the CTD should be provided as applicable.	Information about the solvents for reconstitution and diluents is often not provided in the IMPD, even though it is mentioned in the clinical study protocol.

Table 2: Investigational medicinal products that contain biological/biotechnology derived drug substances.

IMPD section	Applicable Extract from EMA Guidance for Biological IMPs – EMA/CHMP/BWP/534898/2008 rev.1	Comment and recommendations
Drug substance *General comment: In the EU, reference to an ASMF or CEP of the EDQM is neither acceptable nor applicable for biological/biotechnological active substances.*		
2.1.S.2.2 Description of Manufacturing Process and Controls	Any reprocessing during manufacture of the active substance (eg, filter integrity test failure) should be described and justified.	If a statement is not included in the IMPD confirming that there is no reprocessing during the manufacture or purification of the drug substance then comments can be received from certain EU competent authorities.
2.1.S.2.4 Control of Critical Steps and Intermediates	Hold times and storage conditions for process intermediates should be justified and supported by data, if relevant.	It is recommended that stability data are provided in the IMPD to support hold times. This type of information is often requested by some EU competent authorities.
2.1.S.6 Container Closure System	The immediate packaging material used for the active substance should be stated. Possible interaction between the active substance and the immediate packaging should be considered.	See recommendations regarding Section 2.1.S.6 provided in Table 1.
2.1.S.7. Stability	Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. In addition, stability data of relevant development batches or batches manufactured using previous manufacturing processes could be provided. Such batch data may be used in the assignment of shelf life for the active substance provided appropriate justification of representative quality for the clinical trial material is given.	It is recommended that stability data for a batch representative of the manufacturing process of the clinical trial material are included in the IMPD. If the clinical (GMP) batches and development/engineering batches are manufactured at different sites then EU competent authorities may not accept the proposed shelf-life based on stability data obtained with the development/engineering batches without robust data supporting product comparability. Where sponsors wish to extend shelf-life without a substantial amendment then a shelf-life extension plan needs to be provided in the IMPD and accelerated stability data need to be provided to support extrapolation. In the absence of accelerated stability data, an EU competent authority may not allow extrapolation and shelf-life will be restricted to that supported by real-time data. The same principles apply to drug product.
Drug Product		
2.1.P.1 Description and composition of the investigational medicinal product	Refer to extract provided in Table 1.	See recommendations regarding Section 2.1.P.1 provided in Table 1.
2.1.P.3.4 Control of critical steps and intermediates	If holding times are foreseen for process intermediates, periods and storage conditions should be provided and justified by data in terms of physicochemical, biological and microbiological properties. For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable. Test volumes of less than 100 ml may be used if justified.	See recommendations regarding section 3.2.P.3.4 provided in Table 1.
2.1.P.3.5 Process Validation	The state of validation of the aseptic processing should be briefly described, if applicable. Taking into account EudraLex Vol. 4, Annex 13, the validation of sterilising processes should be the same standard as for product authorised for marketing. The dossier should particularly include information directly regarding the product safety, ie, on bioburden and media fill runs.	See recommendations regarding section 3.2.P.3.4 provided in Table 1.
2.1.P.7 Container Closure System	The intended primary packaging to be used for the IMP in the clinical trial should be described. Where appropriate, reference should be made to the relevant pharmacopoeial monograph.	See recommendations regarding Section 2.1.P.7 provided in Table 1.

Table 2: Investigational medicinal products that contain biological/biotechnology derived drug substances (cont.)

IMPD section	Applicable extract from EMA Guidance for Biological IMPs – EMA. CHMP/BWP/534898/2008 rev.1	Comment and recommendations
2.1.P.8 Stability	For preparations intended for use after reconstitution, dilution or mixing, in-use stability data should be presented. These studies are not required if the preparation is to be used immediately after opening or reconstitution. No information regarding synchronisation provided in guideline.	See recommendations regarding Section 2.1.P.8 provided in Table 1. Sponsors should note that if an excipient of animal or animal origin is present in the drug product then the shelf-life of excipients of human or animal origin needs to be synchronised with the expiry date of the medicinal product.[9] Any deviation from this recommendation should be justified in the IMPD or during a scientific advice procedure.
Appendices		
2.1.A.4 Solvents for reconstitution and diluents	For solvents for reconstitution and diluents, the relevant information as indicated in section P of the CTD should be provided as applicable.	See recommendations regarding Section 2.1.A.4 provided in Table 1.

provided in Table 1 and Table 2, common issues are highlighted for both chemical and biological IMPs. For example:

- Not using an EDQM standard term for the pharmaceutical dosage form
- For sterilisation by filtration, the maximum acceptable bioburden prior to the filtration is not stated in the IMPD or the acceptance criterion is not in accordance with EMA recommendations
- Data not provided to confirm that aseptic processing operations were validated
- No confirmation of compliance with Ph Eur monographs for container closure components for both drug substance and drug product
- Shelf-life extension plan for the drug product not in accordance with EMA requirements.

It is highly recommended that US sponsors ask an IMPD subject matter expert to review the IMPD in order to identify potential gaps prior to submissions. For certain types of products, eg, advanced therapy medicinal products (ATMPs) and genetically modified organisms (GMOs), sponsors should take advantage of the opportunity to have scientific advice meetings with EU national competent authorities and/or EMA.

Furthermore, sponsors are recommended to attend EMA workshops focused on CMC requirements such as the EMA workshop on support with regards to quality development in early access approaches.[10] The aim of this workshop, which constitutes a joint collaboration between EU regulators and international partners including US FDA, is to discuss quality challenges and scientific and regulatory approaches that could be used to facilitate development and preparation of robust quality data packages.

It is recommended that US sponsors, if they meet the eligibility criteria, register as a small or medium-sized enterprise (SME) with the EMA, which gives them access to EMA workshops for SMEs focused on quality considerations for IMPs.

In addition, the EMA offers several fee incentives for SMEs including:

- A 90% fee reduction for scientific advice for non-orphan products
- Conditional fee exemption, where the EMA scientific advice is followed and a marketing authorisation application (MAA) is not successful
- Fee deferral until outcome of MAA.

In conclusion, when preparing an IMPD based on an IND it is recommended to follow the recommendations in the EMA quality guidelines for IMPs. Where there is no clear guidance, it is strongly recommended that US sponsors take advantage of the opportunity to have scientific advice meetings to enhance the development process and account for agency requirements and expectations. This ultimately leads to a lower number of GNAs and potential clock stops during the CTA review process and reduces the risk of delays to site activation, first-patient-in milestones and enrolment targets.

References

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