Clinical Trials in the EU/EEA – Focus on CMC Aspects

Posted: September 30, 2013
Jilla Boulas
Delphine Decker
Valerie Pimpaneau
Florence Philippoz

Voisin Consulting Life Sciences

Introduction

Clinical trials testing the Benefit/Risk ratio of Investigational Medicinal Products (IMPs) in the European Union/European Economic Area (EU/EEA) are governed currently by Directive 2001/20/EC [1], defining the requirements for the conduct of clinical trials in the EU. The Directive became effective in 2004 and its implementation in the different EU Member States (MS) occurred by transposition into the national laws of each MS. Approval of clinical trials is under the responsibility of individual MS and involves a thorough evaluation of the products used in the clinical study. The implementation of the Directive has, however, led to different requirements amongst the Competent Authorities (CAs) and Ethics Committees (ECs) of each concerned MS.

Currently, before a clinical trial can be conducted in one EU/EEA MS, a Clinical Trial Application (CTA) has to be submitted and approved by each concerned CA and EC. Detailed description of the content and format of the CTA are provided in the CT-1 guidance updated in March 2010 [2]. This guidance addresses the requirements for an initial submission, the notification of a substantial amendment and the declaration of the end of the trial. More particularly, it includes basic information on the format and content of an Investigational Medicinal Product Dossier (IMPD), and on the format and supporting documents required to implement changes to quality section of the IMPD.
The IMPD is one of the core documents that compose the CTA. The IMPD provides quality and non-clinical data on the IMP, in addition to data from previous clinical trials and human experience to evaluate the benefits and risks associated with the administration of an IMP during the conduct of the clinical trial. The Quality section of the IMPD, describing all aspects of the Chemistry, Manufacturing and Control (CMC) of the product under investigation, plays an important role in ensuring safety and establishing the scientific relevance of the IMP along with already completed non-clinical and clinical studies. The nature of the information and the level of detail to be provided in an IMPD will vary depending on the product type (New Chemical Entity, Biologics, Cell and Gene Therapy Products) and the stage of clinical development. Several guidelines have been prepared by the European Medicines Agency (EMA) to provide further transparency on the content of the quality sections of IMPDs as detailed below.

This article discusses the evolution of the EU regulatory expectations related to the IMPs and how these expectations have influenced the required quality information to include in the IMPD for biological products. First, an overview of regulations, guidelines and events, impacting quality requirements of IMPs, will be presented together with a brief summary of the two procedures currently available for submission of CTAs in the EU. We will then focus on some of the CMC topics requiring special attention when preparing a dossier for a biological product based on our experience with recent submissions.

**Historical Background and Evolution of the EU Clinical Trial Legal Framework**

Below is a chronological presentation of each regulation and guidance document, including the impact they had on the presentation of quality information within the IMPD.

Issued in 2001, Directive 2001/20/EC describes the law and regulations relating to the conduct of clinical trials on IMP for use in humans. While several references to the quality of the IMP are made in this Directive, no specific recommendations on the type of quality information needed by the reviewer are prescribed. In 2004, a Clinical Trials Facilitation Group (CTFG) was established to coordinate the implementation of the Directive across the MS and to promote harmonization of clinical trial assessment decisions and administrative processes across the national CAs.
In March 2006, the company TeGenero sponsored a clinical trial conducted in healthy adults with a novel monoclonal antibody, (TGN1412) developed as an immunotherapeutic aimed at balancing the activity of human immune system. During the first-in-human (FIH) study conducted at Northwick Park Hospital (UK), all six subjects exposed to the IMP (out of eight healthy male volunteers (two under Placebo)) experienced severe systemic adverse reactions, with multiple organ failure soon after intravenous administration of TGN1412. Investigation of the incident showed no obvious errors in the trial. The reaction of the subjects was “completely unexpected” and did not result from lack of quality or non-clinical data. The drug dosage was administered per the protocol reviewed and approved by the Medicines and Healthcare Products Regulatory Agency (MHRA) and Multicenter Research Ethics Committee (MREC).

The most important role of the CMC team is to assure that the IMP is appropriately produced and tested to assure subject safety through defined identity, purity, potency and absence of adventitious agents.

The incident was carefully investigated by an expert scientific group (ESG), set up by the Secretary of State for Health, charged with the responsibility to learn from the incident. The ESG provided recommendations to increase the safety of human subjects in future trials for studies involving high risk IMP [3]. The report identified three categories of IMP which pose high potential risk to humans:

- “Biological molecules with novel mechanism of action
- New agents with a high degree of species-specificity
- New agents with immune system targets”.

The unfortunate events at Northwick Park Hospital resulted in the regulators imposing tight restrictions on high-risk IMPs. Based on the ESG recommendations, EMA released a guideline in September 2007, aimed at assisting sponsors in 1) the transition from preclinical to early clinical development and 2) identification of risk factors to be considered when developing a new IMP. The guideline also includes
recommendations on quality aspects, nonclinical and clinical testing strategies and design for FIH clinical trials [4].

In October 2006, the Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials came into effect [5]. This guideline provides detailed recommendations on the information to be provided in the Quality section of an IMPD. While the scope of this document was initially limited to “chemically defined drug substances, synthetic peptides, herbal substances and radiolabelled substances”, it was often used as a guide for all IMPs, including biologicals. However, important aspects linked to the complexity of biologics were not addressed in the guideline and it was difficult for sponsors of biological IMPs to gauge the appropriate level of details needed for each stage of development.

In April 2012, EMA released the Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials, the first document addressing the quality documentation for a biological IMP (such as proteins, polypeptides, their derivatives, and the products of which they are components [e.g. conjugates]) and aimed at harmonizing the Quality requirements of the IMPD for a biological product to be submitted in the EU [6]. The guideline follows the IMPD structure and is divided into three major technical sections, S-Drug Substance, P-Drug Product and A-Appendices. A fourth section of the guideline describes the considerations of a substantial amendment which is important to know in order to refine the overall CMC development plan. In particular, information is provided related to implementing a shelf life extension of an IMP without the submission of a substantial amendment. The guideline describes an incremental approach for quality information to provide in the IMPD depending on the clinical development phase.

To further harmonize the review and assessment of multinational clinical trials (MN-CT) by CAs in the EU/EEA, the CTFG produced a guideline in November 2009 on a Voluntary Harmonization Procedure (VHP) [7]. The VHP pathway, which has undergone subsequent revisions since then, (latest version dated June 2013), allows for a single initial application for the conduct of multi-national clinical trials (MN-CTs). The VHP application includes only the main core documents and can be submitted in one language (English). The VHP pathway allows for a reliable timeline and harmonized assessment with only one consolidated list of questions, if any, from the different concerned CAs. It only allows a 10-day period for
the sponsor to respond to questions raised by the CAs. This short timeline may be difficult to meet if requests from the CAs involve submission of additional CMC data or documents needed from different sources (e.g. contract manufacturing organizations). These issues should be kept in mind by the sponsor when deciding which pathway to select for their CTA. Depending upon the objectives and regulatory strategy of the sponsor, the classical or the VHP pathway can be followed. Submitting CTAs through the VHP pathway is a good preparation of the coming Regulation.

Despite the evolution of the regulatory environment described above, today, the harmonized approach of Directive 2001/20/EC has only been partially addressed and harmonization of the administrative provisions governing clinical trials in the EU/EEA could only be achieved through a Regulation to be applied in its entirety across the EU. A draft Regulation is currently under discussion between the EU Commission, the EU Council and the EU Parliament [8]. A final document is expected to be released by 2016 and will include a 2-year transition period between the current Directive 2001/20/EC and the new Regulation, once it enters into force. This new Regulation may also influence quality content of the IMPD and review timelines.

**CMC Theory and Practice**

New IMPs and treatments cannot be developed and marketed without adequate scientific data. Much of these data are collected through clinical trials conducted in humans, with emphasis on the safety of the clinical trial subjects. The processes and procedures in place for review of IMPs are designed to minimize harm to subjects while at the same time encouraging and perhaps accelerating the development of new IMPs which can have a positive impact on patient’s health and quality of life. The quality section of an IMPD, part of the CTA package, plays an important role in establishing the scientific justification for conducting studies in humans. Therefore the Quality/CMC team bears part of the responsibility for presenting the scientific evidence and must remain aware of the processes and requirements for submission of a CTA.

Clearly the most important role of the CMC team is to assure that the IMP is appropriately produced and tested to assure subject safety through defined identity, purity, potency and absence of adventitious agents.
The guidelines discussed above provide the framework for the preparation of the IMPD but the actual details included in support of a CTA may vary based on the specific product, and processes involved, (e.g. patient population, severity of the disease). Such factors must be taken into account while assessing the benefit/risk ratio, which, in turn, influences the level of details required in a CTA submission. Below are specific areas that we believe require particular attention as they often lead to questions from the regulators based on our experience with CTA submissions.

**Adventitious Agents**

At any phase of development, the benefits of a drug must outweigh the risks, taking into account the stage of the disease, patient population and quality of the IMP. To evaluate risks, one must look at biosafety properties (e.g. viral safety, endotoxins, microbial contamination, etc.) and impurity profiles (e.g. DNA/RNA, host cell proteins). These quality concerns are often reflected in the nature of the questions raised by the CAs during review of CTA submissions and safety-related issues are the main trigger for rejection of a CTA.

Absence of microbiological contaminant and viral safety risk mitigation need to be demonstrated. A guideline specific to the assessment of viral safety for investigational product was published by the EMA in 2008 which provides an overview of the expectations as well as cross references to the appropriate ICH guidelines [9]. The Note for Guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3) (2011/C 73/01) is critical to consider as it relates to TSE/BSE [10]. A more recent guideline on the use of bovine serum was recently published and is coming into effect in December 2013 [11].

A discussion of risk assessment in the development section of the dossier is strongly recommended, even for an IMP at phase I of development, particularly when mammalian cells are used for the expression system or if raw materials of human or animal origin are part of the process. This assessment will be critical in order to justify the overall multidimensional biosafety strategy and would include data from relevant studies performed throughout the process. For example, viral safety is verified at different levels and includes testing for viruses at the cell bank level, ensuring quality of raw materials of biological origin and providing the appropriate Certificates of Origin and Certificates of Analysis, as well as testing for viruses in the unprocessed bulk, including data on purification steps aimed at reducing viral
contaminants. Additionally assessment/validation of process capacity for removal of viruses and the test method sensitivity to detect contaminants provide supporting data and evidence on steps taken to reduce risk.

Finally, microbial testing occurs at different points in the process and for injectable forms, sterile filtration as well as aseptic filling will be implemented and validated to ensure sterility of the drug products. Therefore, at early phase of development, will to rely on and be asked to include media fill data while awaiting completion of validation studies during later phase of development.

**Potency and Characterization**

Potency of a drug is directly linked to its benefit. Thus, when evaluating the benefit/risk ratio, one must be able to take into account the potency or biological activity of an IMP. The development of a relevant potency assay is critical to success of the CTA as potency is directly linked to the dose and needs to demonstrate the biological activity of the product based on its intended effect. Ideally, potency assays should be related to the clinical response. While the focus of phase I trials is safety, it is important to develop a knowledge of the mode of action of biological activity through characterization studies. It is accepted that complex biological molecules are not always fully understood early on in development. Often times, a single assay may not provide the adequate measure of potency and a combination of several assays (e.g. a binding assay and a functional assay) is often necessary to efficiently assess potency.

If possible, a reliable potency assay should be established early in the development as potency is considered one of the critical quality attributes to monitor. Even so the guideline [6] provides the opportunity to qualify and validate the assays progressively throughout development; validation of critical assays (such as potency and/or purity assays) may be required during the early phase of development. This will ensure that data collected at different stages are reliable and will allow building a strong knowledge of the product early on.

Thorough characterization not only helps in identification of mode of action, but also helps identify physicochemical properties which, in turn, are applied to developing meaningful specifications, assessing
product integrity, stability and establishing controls to verify consistency of the process. All of which add to the benefit/risk assessment performed during review of an IMPD.

For example, due to its important role in pharmacokinetics, in solubility of the glycoproteins and sometimes even in the mode of action, glycosylation is often under high scrutiny by the CAs during review of the CTA. This topic often raises questions and debate around the monitoring of consistency of glycosylation and the possibility to set acceptance criteria. The EMA guideline on the development of monoclonal antibodies recommends specification for each glycoform and while this may not apply fully during clinical development, has to be kept in mind in preparation for the MAA filing.

Purity

Purity of biologics often gives rise to many questions from the CAs. Thus, purity of the IMP should be thoroughly discussed in the IMPD even at early phase I, particularly as it relates to aggregates, particulates, host cell proteins and DNA as well as any potentially toxic compound(s). Some of these impurities have been linked to clinical issues such as immunogenicity, toxicity, and also potential loss of efficacy. Characterization of the impurity profile, including process (media component, column leachates, etc.) and product-related impurities as well as assessment of their removal throughout the process is required. Specifications with acceptance criteria in line with known toxicity limits, process capabilities and non-clinical/clinical outcomes must be implemented and refined as development evolves. Sponsors are expected to have qualification data on methods used to determine HCP, or other impurities to ensure risk evaluation exercise is supported by data. We have experienced many questions focusing on 1) the need to provide spiking studies to demonstrate removal of specific impurities during the drug substance purification process and 2) on the appropriateness of the host cell protein assays for which process specific tests are required at later stages of development.

Process Evolution and Comparability

A consistent manufacturing process is valuable in increasing the benefit/risk ratio of an IMP. Sections describing the processes upstream, downstream, formulation and fill finish should be described clearly within the IMPD with Process Flow Diagram (PFD) laying out each step and their associated control. Critical steps are designated based on the impact on safety or potency and linked through development
data to batch release data. These should be presented along with the associated acceptance criteria which are expected to change as the process evolves through phases of development. Changes to the process such as modification of specific steps, scale up, or manufacturing site transfer should be presented in side by side tables or PFDs and a column explaining the rationale of each change. The product manufactured under the new process will then need to be thoroughly compared to previous non-clinical and clinical materials, and depending on the type of changes, new characterization qualification or validation studies may be required if one intends to rely on data (non-clinical or clinical) from batches made prior to the change. For example, the quality section of an IMPD for a phase I study which has undergone changes after completion of non-clinical studies would include a tabulated discussion of the changes and justification on why the product, made after implementation of the changes, represents the same safety profile as that tested in preclinical studies.

Comparability strategy during clinical development will mainly be safety driven as quality itself is expected to improve throughout the different phases. The key here will be to fully understand the potential impact on the quality of the product and to maintain the bridge between the new process/products and the lots used in prior non-clinical and clinical studies. Comparability exercises often start by a risk assessment, and include process and product comparability using not only release testing but also additional orthogonal methods for further characterization of critical quality attributes.

Even if the changes affect only the drug substance part of the process, comparability considerations should proceed through to the drug product including, when possible, an assessment of the change(s) on product stability to verify that the new process does not induce a different degradation pathway that may not have been detected during release testing.

Well-designed comparability exercises offer value beyond just the regulatory requirements allowing process/product knowledge to be strengthened and an enhanced understanding of the process’ intrinsic variability.

Stability

Generally with biological products, re-test periods are not authorized at the drug substance stage. Thus an expiration date needs to be provided on the basis of the data collected during stability studies.
conducted under proposed storage and accelerated conditions. The guideline [6] provides information on the possibility to extrapolate expiration dates based on real time data collected from relevant storage conditions including stressed conditions.

The stability section of the IMPD will present all data associated with stability batches, along with a discussion of why extrapolation of the data may be justified based on a stability protocol included in the corresponding sections. The selection of assays to monitor stability needs to be justified and methods selected need to be stability-indicating. This justification may be captured during qualification/validation of the analytical methods.

In practice, however, we still see discrepancies between Member States on the extrapolation approach for expiration dating and are sometimes requested to fall back on relying solely on real time data for expiration dating. There is, however, the possibility to submit the stability protocol within the IMPD and, if deemed acceptable by the CA, an extension of shelf life can occur when new time points become available without the submission of a substantial amendment. This is also to be confirmed on a case by case basis with each Member States.

Conclusion

The role of the CMC and the Regulatory Affairs team as well as other departments involved in compiling the information for an IMPD, is to keep safety of the clinical trial subjects as the top priority for any study. Therefore, each CTA must provide the reviewers at the CA with the assurance that 1) the study will not expose the subjects to unjustified risk and that 2) the subjects may potentially benefit from the use of the IMP (with the exception of healthy volunteer studies where the subjects are not necessarily expected to experience a clinical benefit from the IMP).

When compiling the quality section of the IMPD, knowledge of the timelines and requirements associated with different procedures is important. Some clear and obvious points to remember when preparing an IMPD include the use of the CTD format as this is a worldwide accepted format. The decision on which information is required at each phase of development is dependent on the nature of the IMP and the associated risks. As a result of lessons learned from events, such as Northwick Park Hospital, an FIH clinical trial represents a much higher risk than those that have already been used in previous/similar
studies. Therefore quality section of the IMPD, for an IMP to be used in an FIH trial, would include more
detailed information on characterization, qualified/validated potency and impurities methods, accuracy of
dosage and potential comparability discussion.

The risk associated with biological IMPs may be quite different from that of new chemical entities. For this
reason the guidance document specific to the quality of biological IMPs satisfies a long-awaited need for
sponsors. The guidance also provides examples of quality changes which would require substantial
amendments and are important to take into account while designing the overall CMC strategy.

Based on our experience, the quality issues raised in a CTA are the same irrespective of the procedure
(classical approach or VHP). The CMC expectation is not dependent on the procedure but rather on the
individual countries involved, the nature of product and the phase of the clinical trial. These factors play a
role in determining the level of details required for an IMPD. The cross functional efforts of different
teams, i.e. CMC (including Manufacturing, Quality, Supply Chain, etc.), Non-Clinical, Clinical, and
Regulatory Affairs groups are essential in ensuring that the appropriate IMP gets to the right subject at
the right time. The vehicle by which we get to that point is through product development founded on good
science reflected in a well-prepared and well-justified IMPD.

References

1. DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001 on
the approximation of the laws, regulations and administrative provisions of the Member States relating to
the implementation of good clinical practice in the conduct of clinical trials on medicinal products for
2. Detailed guidance on the request to the competent authorities for authorization of a clinical trial on a
medicinal product for human use, the notification of substantial amendments and the declaration of the
3. EXPERT SCIENTIFIC GROUP ON PHASE ONE CLINICAL TRIALS, FINAL REPORT- 30th November
4. Guideline on strategies to identify and mitigate risks for firstin- human clinical trials with investigational
medicinal products - EMEA/CHMP/SWP/28367/07,


**Jilla K. Boulas** is a Director at Voisin Consulting office in Cambridge, Massachusetts, USA; involved in assisting/consulting clients in the design and implementation of product development plans from a CMC perspective. Recent activities include preparation of IMPD, Scientific Advice package, IND, NDA, BLA, supplements/variations, comparability reports, assessment and evaluation of changes for impact on clinical and licensed products.

**Delphine Decker** is a Director managing the clinical trial resources at VCLS. Delphine is responsible for the regulatory set-up and management of clinical trials, from the initial application to the submission of the clinical study report. She has an extensive technical expertise in clinical trial regulations, including in the recent Voluntary Harmonized Procedure (VHP), and associated country-specific requirements, and has broad experience in various trial phases, product types, indications and geographical areas.
Florence Philippoz is a Director at Voisin Consulting office in Lausanne, Switzerland. She provides scientific, technical and regulatory expertise in projects involving the development of Chemistry Manufacturing and Control (CMC). With a strong industrial experience in Quality Assurance, Quality Control and Analytical Development, she is involved in reviewing or authoring regulatory documents such as CMC sections of IMPD/IND, IB, Briefing Packages for Scientific Advice, CTD Module 3, and Quality Overall Summary of MAA/ BLA/NDA.

Valerie Pimpaneau is Senior Director and manages the CMC group within VCLS. She contributes to the design of the CMC strategy for Biologics, Gene and Cell Therapy. Working at the interface between technical and regulatory teams, she coordinates all CMC activities in line with the product development phases. This includes preparation of regulatory submissions, associated technical reports and interaction with