Clinical trials in Europe: an overview of quality requirements

Authors
Aine Kane, Julie Williams and Lydia Yeo, Pfizer Global Research & Development, UK

Key words

Abstract
This article aims to provide a broad overview of the regulatory framework relevant to the quality and Good Manufacturing Practice aspects of investigational medicinal product regulation in Europe, describing the overarching Clinical Trials Directive (2001/20/EC) and supporting European and national quality guidelines. A perspective is given on the high level texts, and the guidance and legislation developed under this umbrella. A brief description of intended function, interrelationships and development history to date is provided.

Some examples of actual experiences with the interpretation and application of quality requirements for the Investigational Medicinal Product Dossier across Europe are shared. Possible developments to further enhance harmonisation of quality requirements in Europe and to ensure continued attractiveness of Europe as an environment for clinical research are discussed.

The Clinical Trials Directive – origin and intent
Directive 2001/20/EC, commonly known as the Clinical Trials Directive, was published in its final form in the Official Journal of the European Communities on May 1, 2001. The main impetus behind development of the Directive had been to harmonise Good Clinical Practice requirements in Europe, and introduce Good Manufacturing Practice expectations to clinical trials supplies, also known as investigational medicinal products (IMPs). In addition, there was a broader intent to harmonise supportive data requirements for clinical trials submissions across Europe.

In terms of implementation, the goal was that, from the May 1, 2001 effective date, EU Member States (MSs) would have a maximum of two years to transpose the Directive into their national legislation, and a further one year to implement the resultant regulatory requirements. While this has largely been achieved (and has included 10 additional EU accession countries) our understanding is that implementation is still ongoing in some MSs.

Transposition – necessity and impact
Harmonisation of requirements for clinical studies across Europe was, and is, a key goal of the Clinical Trials Directive and subsequent guidance documents. However, a required implementation step of Directive 2001/20/EC has been transposition into national MS legislation. It may have been anticipated, therefore, that a degree of divergence might result from the Directive’s transposition.

As transposition has progressed, it has become apparent that the combined effect of varying interpretation of the Directive text, together with superimposition of new requirements onto existing MS legislation has led to a more divergent picture than might have been foreseen. Currently, from a quality perspective, our experience is that a number of key divergent areas exist, which could usefully be reconciled. We expand upon this topic later in this article.

Key quality content
A number of articles in the Clinical Trials Directive 2001/20/EC pertain to the quality of the IMP; these are highlighted in Table 1.

Table 1: Articles within the Clinical Trials Directive 2001/20/EC pertaining to quality of the IMP

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<th>Article</th>
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<td>9</td>
<td>(8) In consultation with Member States, the Commission shall draw up and publish detailed guidance on: (a) the format and contents of the request referred to in paragraph 2 as well as the documentation to be submitted to support that request, on the quality and manufacture of the investigational medicinal product, any toxicological and pharmacological tests, the protocol and clinical information on the investigational medicinal product including the investigator’s brochure; (b) the presentation and content of the proposed amendment referred to in point (a) of Article 10 on substantial amendments made to the protocol; (c) the declaration of the end of the clinical trial.</td>
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As indicated in the articles listed above, a number of supporting guidelines and legislative texts have been developed under the umbrella of the 2001/20/EC, which are now published collectively within EudraLex - Volume 10².

Key quality/Good Manufacturing Practice texts include:


b. Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial. Revision 2 - Final version.

c. Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use. Revision 1 - Final version.


e. EudraLex - Volume 10: Clinical trials guidelines, Notice to applicants, Questions & answers on clinical trial documents.


g. Community basic format for manufacturing authorisation; Community basic format for manufacturers/importers.

h. Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.

**Quality-specific guidance**

Initially, the high-level, pan-European guideline labelled as “b” above constituted the total regulatory guidance for quality aspects of clinical trials submissions. This guideline provided guidance on the format of the Investigational Medicinal Product Dossier (IMPD), but did not set out detailed expectations on the content and level of data expected. Consequently, industry and regulators recognised the need for a focused, quality-specific guidance to bridge the gap between this high-level text and the degree of detail helpful to support clinical trials submissions. The principal objective was to define harmonised requirements for the documentation to be submitted throughout the European community.

In 2004, the European Medicines Agency’s (EMEA’s) Committee for Proprietary Medicinal Products (CPMP) – now the Committee for Medicinal Products for Human Use (CHMP) – proposed development of a specific quality guideline for IMPs via publication of a Concept Paper (CPMP/QWP/1542/04). Guideline development was supported by interested parties, and a guideline focusing on quality data expectations subsequently developed via the EMEA’s consultation process. Based on the high number of comments received, it took several draft versions and two hearings with industry associations and other stakeholders before the guideline was adopted by the CHMP in March 2006, and published in Volume 10: Clinical trials, Notice to applicants, coming into force in October 2006. The final guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials, is also known as the “IMPD-Q” guideline.

The IMPD-Q guideline has been useful for applicants and has had a positive impact on attempting to harmonise quality clinical trial requirements across the EU. Representatives from national competent authorities (NCAs) have commented that the quality of IMPDs has improved and consequently they have fewer requests for additional information. The guideline articulates the content and typical data expectations for the different phases of development and takes into consideration that less data will be available at early stages of development. The guidance around changes to the IMP and where a substantial amendment may be needed provides some helpful examples of typical CMC (Chemistry, Manufacture and Controls) changes and whether these could require submission of a substantial amendment. Importantly, the guideline sets a clear expectation that the sponsor is responsible for assessment of a change to the IMP and its potential impact on:

- The safety or physical or mental integrity of the patients
- The scientific values of the trial
- The conduct or management of the trial
- The quality or safety of any IMP used in the trial.

Overall, the availability of the IMPD-Q guideline has been very welcome.
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Areas with potential for improvement

In addition to this overall positive feedback, there is some concern that there has been a general escalation in data requirements for EU clinical trial submissions compared to other regions, particularly the USA. Moreover, differing interpretation of the guideline is leading to divergent regulatory requirements between MSs, which can hinder rapid and efficient preparation of clinical trial applications for global clinical studies. Many cases where NCAs are requesting additional or different information in the IMPD could be improved by greater education and adoption of the guideline principles. The industry would assert that the NCA requests should not contradict IMPD-Q requirements.

Some examples of key areas of concern are detailed further below:

1. Method validation expectations at different phases of development

The IMPD-Q guideline confirms that although some validation information is required to show the suitability of analytical methods at Phase I and II, method validation should not be expected until later in development. In contrast, some NCAs are requesting extensive detail on analytical method validation early in development.

2. Shelf life extensions

One particular area of concern is that industry is experiencing differing expectations from MSs in terms of assignment of shelf life to IMPs based on the extrapolation of stability data. Some MSs impose International Conference on Harmonisation (ICH) stability data requirements upon clinical trials which we believe is inappropriate and contrary to the stated principles in the guideline. One of the key consequences of restricting the shelf life of an IMP until long-term stability data are generated is that it may limit the ability of a company to conduct clinical trials in those countries until later in development.

There has also been much discussion around the strategy for updating shelf life throughout development and consequent updates to the IMPD. Arguably, shelf life is the most frequently encountered update to an IMPD during development and the preference of many applicants would be to update shelf life, as more stability data are generated, without a need for submission of a substantial amendment. This approach is addressed in the IMPD-Q guideline and is accepted by MSs if the stability strategy and shelf life assignment are clearly and adequately presented in the initial IMPD. To avoid the need for subsequent substantial amendments, the IMPD should contain the proposed specification and provide a clear explanation of how extrapolation is/will be applied to assign the shelf life.

3. Specifications

There are often differences in the agency expectations for specifications versus the applicant. One area which requires addressing is the basis on which acceptance criteria for impurities should be set. Industry considers that limits should be supported by the impurity profiles of batches of active substance used in non-clinical/clinical studies and that at early stages of development compliance with ICH requirements should not be mandatory. Competent authorities, however, encourage applicants to provide as much information and rationale as they can, to justify their specifications.

4. Site-specific batch data and certificates of analysis

The IMPD-Q guidance clearly states that results or certificates of analysis for batches representative of the IMP to be used in the clinical study should be provided. However, some MSs insist on batch specific certificates of analysis for formulated IMP or batch data for each manufacturing site listed, despite the flexibility allowed by the IMPD-Q guidance including the provision of proposed manufacturing sites. On occasions, the data on the clinical batch may not be available at the time of the IMPD submission, resulting in the need to provide a substantial amendment to include batch data for a proposed manufacturing site. This results in additional bureaucracy for the applicant without contributing to patient safety.

5. Substantial amendments versus non-substantial amendments

As outlined in guideline “h” above, the responsibility for determining whether a change is substantial or non-substantial lies with the sponsor and should be decided on a case by case basis. This guideline and Chapter I of EC guideline “b” above, provide a list of criteria to guide sponsors in the determination of appropriate classification of amendments.

This is welcomed by industry and is considered appropriate. However, the French agency has very recently issued its own guidance on substantial versus non-substantial amendments. While this is “hot off the press” and needs to be fully reviewed before the authors can comment on it, it perhaps raises some concern that national guidance is being developed that could not be in line with harmonisation across EU.

In line with guidelines, there is no requirement for a sponsor to notify the NCA or Ethics Committee of non-substantial amendments, however, they should be recorded and included in the annual update to the Investigator’s Brochure (IB), if appropriate. However, we have recent experience of one NCA requesting routine reporting of all non-substantial amendments, which is an additional, and duplicative, administrative burden since non-substantial amendments are already subject to GMP inspection and, by definition, are low risk.

6. Investigational medicinal products and non-investigational medicinal products (NIMPs)

A number of MSs interpret the EU recommendations on what constitutes an IMP and an NIMP differently, which leads to additional regulatory submission requirements in some MSs.

As context, NIMPs are used alongside IMPs in clinical trials for preventive, diagnostic or therapeutic reasons and/or to ensure that adequate medical care is provided for the subject. They may also be used in accordance with the clinical protocol to induce a physiological response.

The European guideline Definition of investigational medicinal products (IMPs), Definition of non-investigational medicinal products (NIMPs), which can be found in EudraLex - Volume 10, recommends that the sponsor should use a NIMP with a marketing authorisation (MA) in the MS concerned. If this recommendation cannot be met then it is acceptable to use a NIMP with an MA in another MS or in exceptional circumstances a NIMP without an MA in the EU.
However, a number of MSs (listed in the guideline) will only allow therapies such as rescue medication, challenge agents, and medicines used to assess primary end-points to be classed as NIMPs, where the first recommendation of the guideline is met. The second and third options are not recognised, resulting in therapies being considered as IMPs, with a requirement to file all the usual data required in support of an IMP. This represents an additional burden to sponsors as a result of non-aligned regulatory requirements.

**Latest developments**

**Steps to clarify and align guidance**

Following recent regulatory/industry discussions, a proposal has been developed for a question and answer document, aimed at clarifying the IMPD-Q guideline data expectations to reconcile divergent positions. The opportunity and development of this document is being considered by the EMEA Quality Working Party.

**EFPIA proposal – Community Clinical Trial Authorisation (CTA)**

The European Federation of Pharmaceutical Industries and Associations (EFPIA) is developing a proposal to introduce an optional Community CTA submission and approval process, aimed at providing a possible pan-EU alternative to the current CTA system. A key objective is to reduce the bureaucratic burden for both industry and regulators, with no negative impact upon subject or patient safety. It is hoped that, by providing a streamlined alternative to the current clinical trial system, the proposed system will act to enhance the attractiveness of Europe as a location for clinical trials, moving forward.

**Proposal for EU IMP-biologicals guidance**

Biotechnology products are excluded from the scope of the CHMP IMPD-Q therefore, development of a guideline focusing on quality data expectations for biological IMPs has recently been proposed. A draft guideline is expected to be adopted in 2009 by the Biologics Working Party/CHMP, followed by a six-month consultation period. It is hoped that the lessons learned with the initial quality guideline will be applied here so that aligned, and appropriate regulatory expectations result.

**Conduct of exploratory trials – guidance development in Belgium**

The Belgian regulatory authority recently issued guidance covering the conduct of exploratory trials in Belgium. Such studies do not have any therapeutic or diagnostic intent and limit human exposure in terms of dose, time and number of participants. This guidance is a working document and has been prepared in anticipation of development of guidance at a European level. It provides a number of recommendations in order to provide a framework for preparing and evaluating exploratory clinical trial applications for studies to be conducted in Belgium. The quality evaluation of such submissions is conducted according to the guidelines “f” and “h” listed above as well as:

i. Note for Guidance on Good Manufacturing Practice for active pharmaceutical ingredients [CPMP/ICH/4106/00]

j. Note for Guidance on minimising the risk of transmitting animal spongiform encephalopathy via human and veterinary medicinal products [EMEA/401/01]

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**Focus**
However, the expectation is that the quality requirements will be less demanding than those expected for a Phase I trial as exposure is limited and there is no intent to reach doses that could cause toxicity. In principle the same guidance would apply to biological products.

**Conclusion**

Overall, the Clinical Trials Directive and its associated supportive guidance have had a positive impact on the quality aspects of clinical trials in Europe. The development of the CHMP IMPD-Q guideline was supported by an open and effective collaboration between regulatory agencies, industry and other stakeholders. We believe that there is a genuine desire and commitment to improve and retain attractiveness of the EU for clinical research and development without compromising on volunteer and patient safety.

But we do continue to have concerns that the Clinical Trials Directive has resulted in a net escalation in data requirements, without the true harmonisation of expectations or fully aligned implementation across the EU that was expected. Thus it is important that regulators, industry and other stakeholders jointly continue the dialogue and work to ensure appropriate data expectations for IMPDs and to improve harmonisation across Europe.

Any future changes to the regulatory framework, whilst maintaining protection of the patient or subject as the primary objective, should focus on a less bureaucratic and more scientific and risk-management based approach in order to ensure the EU remains an attractive environment for clinical research.

Our vision is for an aligned set of quality and GMP data expectations, founded upon science and risk-management principles, linked with an efficient clinical trials submission, approval and maintenance process which together provide an attractive environment for continued medicines development in Europe.

**References**
