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The European Clinical Trials Directive—A Regulatory Approach for Filing Drug Substance Information

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OVERVIEW

The European Clinical Trials Directive was first proposed as a White Paper in 1991 and published as a draft directive in 1997 in the European Union (Meader, 2004). The finalized directive was published in the Official Journal of the European Commission on May 1, 2001 (Official Journal of the European Communities, 2001). The directive contains 24 separate articles including Article 1, the Scope of the Directive, which indicates that the regulatory requirements of the directive pertain to all phases of clinical studies in human subjects. Article 13, entitled Manufacture and Import of Investigational Medicinal Products, is of particular interest to the Regulatory CMC (Chemistry, Manufacturing, and Controls) Scientist. Some important features of Article 13 include the requirements that: 1) the manufacturer possess a manufacturing authorization for the investigational medicinal product, 2) a qualified person is employed for the release of the investigational product, and 3) the investigational product is manufactured in compliance with European Union Good Manufacturing Practices (EU GMPs) (Official Journal of the European Communities, 2003). In April, 2004, the European Commission, Enterprise Directorate-General issued a revised detailed guidance for the request for authorization of a clinical trial on medicinal products for human use (European Commission, 2004). The guidance details the procedure (format and content) to request a clinical trial authorization, and the procedures for the notification of amendments and the declaration of the end of a clinical trial. Recently, an additional guidance was issued for consultation by the European Medicines Agency (EMEA) concerning the general chemical and pharmaceutical requirements for investigational medicinal products (European Medicines Agency, 2004).

This article describes a regulatory approach with detailed guidance on specific sections for filing CMC information concerning the drug substance in Phases 1, 2, and 3. The approach details the critical drug substance information necessary to support the investigational medicinal product dossier (IMPD) in each clinical study phase.

Finally, the approach suggested here also supports the filing requirements for investigational new drug applications (IND) in the United States (U.S.

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Department of Health and Human Services, 1995, 2003). The article is divided according to the sections proposed in the European Commission, Enterprise Directorate-General detailed guidance (European Commission, 2004). Suggested text is provided in italics for a hypothetical drug substance.

INTRODUCTION

For all applications, a statement should be provided on the safety of the clinical trial material. In general, the statement should reflect that neither the chemistry of the investigational drug product nor its manufacture presents potential risk in the clinical setting. The amelioration of any potential risk associated with the chemistry of the investigational drug product should be discussed as well as any differences in chemistry/manufacturing between the investigational drug product proposed for clinical use and the material used in the animal toxicology studies.

European health authorities do not allow for a cross-reference to Drug Master Files for the IMPD as is permitted under an IND in the United States (U.S. Department of Health and Human Services, 1989). Information on the drug substance must be provided directly in the IMPD. If the drug substance is described in a well-known pharmacopoeia such as the European Pharmacopoeia (PhEur), the British Pharmacopoeia (BP), or the United States Pharmacopeia (USP), a statement that the drug substance to be used is tested for compliance with the relevant pharmacopoeial monograph should be provided in the IMPD along with analytical data for the lots submitted. A manufacturer of drug substance may apply for certification of compliance with monographs of the European Pharmacopoeia for a compendial drug substance (European Pharmacopoeia, 2001). In this instance, a reference to the certificate number should be provided in the IMPD. If more than one active drug substance is included in the submission, include appropriate information on the additional drug substance in a duplicate drug substance section.

GENERAL INFORMATION

Nomenclature

The chemical name of the drug substance is provided. IUPAC (International Union of Pure and Applied Chemistry) nomenclature should be employed. The descriptive name of the drug substance is provided in addition to the International Non-proprietary Name (INN), compendial name or other non-proprietary names, if available. The laboratory code name, the research number and the Chemical Abstracts Service registry number are noted.

Descriptive name of the drug substance(s): Drug Substance X
INN: Insert text or indicate "Not Available"
Compendial name: Insert text or indicate "Not Available"
Chemical name(s): Insert text
Company or laboratory code: Insert code
Research number: Insert number
Other non-proprietary names: e.g., British Approved Name (BAN), United States Adopted Name (USAN), Japanese Approved Name (JAN)
Chemical Abstracts Service (CAS) registry number: Insert number

Structure

The following information should be detailed:

- Structural formula (diagrammatically) with relative and absolute stereochemistry
- Molecular formula
- Relative molecular mass/molecular weight
- Stereochemistry

General Properties

List all physico-chemical properties that are appropriate for the drug substance and dosage form (e.g., physical form, polymorphic form, particle size distribution, partition coefficient, solubility, etc.). Include the batch number on which the properties were determined. The level of detail should provide an overview of basic properties such as solubility and any additional physico-chemical properties that can influence the behavior of the drug product. Characterization of the drug substance is part of an overall strategy to develop drug products that are safe and efficacious (Pritchard et al., 2003).

MANUFACTURE

Manufacturer(s)

Provide a list of all firms associated with the manufacture and control of the drug substance

including contract laboratories for quality control and stability testing.

The drug substance is manufactured, packaged, tested, and released at:

Company name: Insert legal name of manufacturing company
Complete address: Insert address of manufacturing facility

If multiple sites are involved in the drug substance manufacture, list each site and indicate which steps are performed at each site.

Description of Manufacturing Process and Process Controls

1. Flowchart (Diagram)

   Provide a Flow Diagram(s), which includes:

   - Chemical structures of starting materials, intermediates, reagents, and the drug substance including an indication of the stereochemistry
   - Compound numbers of starting materials and intermediates
   - Solvents and catalysts can be presented here or listed separately in tabular format with an indication of which steps include use of these reagents

2. Description

   The degree of manufacturing information provided is dependent upon the development phase of the clinical program. For Phase 1/2, a brief description is presented.

   For Phase 3, provide a general step-by-step description of the synthesis, including the final recrystalization of the drug substance. It is preferable to number each step. Typically, information concerning: batch size (range), type of reaction vessel, relative ratios of reactants, catalyst, and reagents, general operating conditions (time, temperature), and in-process controls are not included in the description as these aspects of the synthesis will continue to undergo development. An overview of key changes to the synthesis process should be given with each update of the IMPD. If different polymorphic forms (Brittain et al., 1991) are possible, indicate which polymorphic form is obtained via the synthesis method proposed.

TABLE 1 **Overview of Relevant Batches of Drug Substance X and Corresponding Synthesis Methods**

Batch	Synthesis method	Batch usage
482395	1	Tox study #63824
482396	2	Proposed clinical study

Results of batch analysis of each batch are provided in Batch Analyses.

The following text can be used as a starting point to describe the differences between synthetic routes which have been previously filed to the IMPD or are provided as supportive information for the filing (e.g. stability lots).

Drug substance X is made through a series of organic synthesis reactions followed by purification, sieving and milling. During the development of the drug substance synthesis, two synthesis methods (Synthesis Method 1 and Synthesis Method 2) were used. In Synthesis Method 2, minor changes were made including the addition of certain reagents in the early steps of the synthesis, elimination of the use of a catalyst and the use of a different co-solvent for recrystalization. Synthesis Method 2 also included the addition of a purification step for the drug substance via an additional recrystallization step.

An overview of relevant batches made with each synthesis method is provided in Table 1. The batch synthesized with Synthesis Method 1 has been used for stability and toxicological studies. The batch made using Synthesis Method 2 is used for stability and is representative for batches used in the proposed clinical study.

Insert a conclusion on the batch analysis data e.g., no differences are observed in the purity between the different drug substance batches produced using the two synthesis methods described. If differences exist, explain the differences and their relevance.

Control of Materials

1. Starting materials

   This information is typically not required for Phase 1 or 2. For Phase 3, only brief descriptive information pertaining to the test parameter, acceptance criteria and test method are given as

TABLE 2 Acceptance Criteria and Testing of the Starting Materials for Drug Substance X

Starting materials	Test parameter	Acceptance criteria	Test method
1-Napthol	Assay	90.0–110.0%	GC

shown in Table 2 below. Control of materials include such tests as gas chromatography (GC), high performance liquid chromatography (HPLC), and capillary electrophoresis (CE).

2. Solvents and reagents

   Insert a list of all solvents, reagents used during the synthesis of the drug substance and identify the process step where each material is used (see Table 3).

3. Catalysts

   Insert a list of all catalysts used during the synthesis of the drug substance and identify the process step where each catalysts is used.

Control of Critical Steps and Intermediates

Control of critical steps and intermediates information is typically not required for Phase 1 or 2. For Phase 3, only brief descriptive information pertaining to the test parameter, acceptance criteria and test method for the critical intermediates are given as shown in Table 4 below.

Process Validation and/or Evaluation

Process validation information is not applicable for development phases and is not filed in the IMPD. A statement indicating a commitment to address this aspect of the file in the future market application can be made.

TABLE 3 Solvents and Reagents Used During the Manufacture of Drug Substance X

Solvent/regent	Process step
Methanol	1
Isopropanol	2
Ethanol	4

TABLE 4 Acceptance Criteria and Testing of the Critical Intermediates

Critical intermediate	Test parameter	Acceptance criteria	Test method
I001234	Assay	95.0–105.0%	GC

Manufacturing Process Development

Typically, manufacturing process development information is not applicable for development phases and is not filed in the IMPD. A statement indicating a commitment to address this aspect of the file in the future market application can be made. For complex technology, it may be appropriate to include some information on process development.

CHARACTERIZATION

Elucidation of Structure and Other Characteristics

Structural elucidation studies may include elemental analysis, mass spectrometry, liquid chromatography/mass spectrometry (LC/MS) (Lim & Lord, 2002), Nuclear Magnetic Resonance (NMR) spectroscopy (Reddy et al., 2002; Streng, 1997), UV-visible spectroscopy, infrared spectroscopy (IR), Fourier Transform-IR spectroscopy (Griesser & Burger, 1993; Rollinger & Burger, 2002), stereochemical analysis (Doyle et al., 1997), configurational/conformational analysis (Sebag et al., 2001), X-ray analysis, degradative analysis, and chromatographic analysis. The references sited provide examples of the analysis that may be needed to support the structure elucidation aspects of the IMPD.

The molecular weight, the empirical formula and the structure of Drug Substance X were confirmed using the following techniques.

- UV-Visible Spectroscopy
- Infrared Spectroscopy
- Mass Spectrometry (MS)
- ^{1}H-NMR
- ^{13}C-NMR

Insert spectra (UV/IR/NMR), fragmentation schemes (MS), and tables of assignments (explanation of the different observed adsorption bands—UV/IR,

or of fragment ions—MS, or of chemical shifts—NMR) for each technique. A statement should be included that indicates that the spectra support the proposed structure.

Results and discussion on polymorphic behavior of the drug substance, including its impact on the behavior of the drug product should be provided.

The following studies were performed to identify the potential polymorphic forms of the drug substance:

- X-ray Diffraction
- Thermal Analysis
- Infrared Spectroscopy
- Differential Scanning Calorimetry

These measurements were performed on batch number 482395. This batch is also designated as the chemical reference compound. The spectra support the proposed structure.

Impurities

Impurities of drug substances may be classified into the following categories (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2002):

1. Organic Impurities

   Organic impurities are produced during the manufacturing process and during the storage of the drug substance (degradation products). Organic impurities may include:

   - Starting materials
   - By-products
   - Intermediates
   - Degradation Products
   - Reagents, ligands, and catalysts

   The organic impurity profile of the drug substance given in the IMPD includes the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance. An overview of the actual and potential impurities should be given including an overview of the chemical structures. The impurity profile of all batches pertinent to the clinical study (including toxicology study batches) can be given in S.4.4 and a cross-reference to S.4.4 can be given here. A comparison of impurity profiles across these lots is made to demonstrate that appropriate toxicological qualification has been performed on all impurities present in the clinical batch.

2. Inorganic Impurities

   Inorganic impurities result from the manufacturing process and include:

   - Reagents, ligands, and catalysts
   - Residual metals
   - Salts
   - Other materials (e.g., filter aids, charcoal)

   Metal catalysts are often employed in synthetic processes and should be controlled. A draft guidance for medicinal products is available (Committee for Proprietary Medicinal Products, 2002) and although, not strictly applicable to investigational drugs, may be helpful in setting investigational specifications.

   An inorganic impurity profile should be available for each drug substance lot used in toxicological evaluations, and for the lot proposed to be used in the clinical study.

3. Residual Solvents

   Solvents are used in the preparation of solutions or suspensions during the synthesis of a new drug substance. The maximum levels of residual solvents should be limited by ICH Q3C guidance (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, 1997). Information on residual solvents should be available for all of the lots discussed above.

1. Organic Impurities

   The organic impurity profile of the drug substance includes the actual and potential impurities most likely to arise during the synthesis, purification, and storage of the drug substance. Potential organic impurities are also suggested by degradation studies of the drug substance. The actual and potential impurities, which are structurally related to the drug substance, are presented below.

   The chemical structure(s) and origin from each actual and potential impurity, if available would be inserted here.

   The impurity profile of Drug Substance X was established from several batches that were synthesized according to the two routes of synthesis described in Description of Manufacturing Process

TABLE 5 Chromatographic Purity of Drug Substance X

Batch no.	Assay and related compounds (HPLC)			Enantiomeric purity (CE)	Toxicology study no./ study description
	Drug substance (%)	Impurity 1	Impurity 2	Area %	
482395	98.5	0.2%	0.3%	97.5%	63824
482396	98.9	0.1%	0.2%	98.3%	Proposed clinical study

and Process Controls. Only drug substance batches manufactured with Synthesis Method 2 are representative for the drug substance that will be used in upcoming clinical trials.

Table 5 provides a summary of the organic impurity information to support use of the clinical product. The table also identifies the batches used in toxicology studies and provides the corresponding toxicology study numbers.

Impurity 1 and Impurity 2 are qualified at a level of 1% based upon the toxicological studies described in the preclinical section of the IMPD.

The results show that the individual impurity levels remain below the qualification level of 1% and the acceptance criteria of 0.5%.

The results show that the total impurity levels remain below the acceptance criteria of 2.0%.

Potential degradation products are monitored with stability indicating methods, which are described in Analytical Procedures.

2. Inorganic Impurities

   The actual levels of heavy metals present in batches of Drug Substance X are consistently below 20 ppm.

   The actual levels of sulphated ash in batches of Drug Substance X are consistently below 0.5%.

3. Residual Solvents

   The levels of residual solvents present in batches of Drug Substance X are summarized in Table 6.

TABLE 6 Levels of Residual Solvents in Batches for Drug Substance X

Batch No.	Methanol	Ethanol	Isopropanol
482395	420 ppm	280 ppm	250 ppm
482396[a]	350 ppm	230 ppm	270 ppm

[a]Batch proposed for clinical study.

The actual levels of the residual solvents in batches of Drug Substance X are consistently below the proposed acceptance criteria.

4. Water

   If applicable, information on the water content of the drug substance can be provided. Water content is relevant for the case of a hygroscopic drug substance (Reffner, 2003).

CONTROL OF DRUG SUBSTANCE

Specification

Drug Substance X will be controlled in accordance with the specifications and methodology outlined in Table 7. The tests and specifications selected are intended to ensure the identity, purity, quality, and strength of this drug substance.

TABLE 7 Test Parameters, Acceptance Criteria, and Testing Methods of Drug Substance X

Test parameter	Acceptance criteria	Test methods
Appearance	White crystalline powder	Visual
Identification	Matches reference standard	IR
Assay	97.0–103.0%	HPLC
Impurity 1	<0.5%	HPLC
Impurity 2	<0.5%	HPLC
Total impurities	<1.5%	HPLC
Loss on drying	<1.0%	Gravimetric
Residue on ignition	<1.0%	PhEur
Residual solvents:		GC
Methanol	3000 ppm	
Ethanol	5000 ppm	
Isopropanol	5000 ppm	

TABLE 8 Operating Conditions of the Assay and Impurity HPLC Method

Parameter	Conditions
Column	Reversed phase C18, 5 μm 4.6 × 10 mm
Column temperature	30°C
Flow rate	2.0 mL/min
Injection volume	10 μL
Detection wavelength	UV at 254 nm
Mobile phase	50/50 methanol/water
Elution mode	Isocratic
Analysis time	20 minutes

The operating conditions may be adapted in order to meet the system suitability requirements.

TABLE 10 Operating Conditions of the Capillary Electrophoresis Stereoisomeric Purity Method

Parameter	Conditions
Column	Uncoated fused silica
Column temperature	50°C
Injection mode	Hydrodynamic
Detection wavelength	UV at × 254 nm
Background electrolyte	Heptakis (2,3,6-tri-O-methyl) β-cyclodextrin in a mixture of H_3PO_4 and triethanolamine

The operating conditions may be adapted in order to meet the system suitability requirements.

Analytical Procedures

A brief description of the analytical methods used to control the drug substance is given. This information may be provided in tabular format.

1. Test Procedure for Quantitative Determination and Identification of the Active Ingredient and Its Structurally Related Impurities (HPLC)

   The operating conditions for the HPLC method are provided in Table 8.

   The chromatographic characteristics are outlined in Table 9.
2. Test Procedure for the Determination of the Stereo Isomeric Purity (CE)

   The operating conditions for the CE method are provided in Table 10.

   The chromatographic characteristics for the CE method are outlined in Table 11.
3. Test Procedure for the Determination of Residual Solvents (Gas Chromatography)

   The operating conditions for the GC method are provided in Table 12.

The relative elution sequence is outlined in Table 13.

Validation of Analytical Procedures

For all phases, a summary of the validation of the analytical methods should be provided in tabular format. The example below is for the HPLC procedure for the assay and determination of impurities.

A summary of the results of the assay and impurity HPLC method validation is given below:

Specificity: The specificity for Drug Substance X and related compounds has been checked by means of representative samples.

Linearity: The correlation coefficient for Drug Substance X is ≥ 0.99 over the range of 0.2 to 1.0 mg/mL. The correlation coefficient for the related compounds is ≥ 0.99 over the range 0f 0.002 to 0.02 mg/mL.

Precision: The system repeatability is tested with Drug Substance X and meets a RSD criterion that is $\leq 2.0\%$.

TABLE 9 Chromatographic Characteristics

Compound	Relative retention time	Comments
Drug substance X	1.0	Main compound
Impurity 1	1.2	Degradation compound
Impurity 2	1.4	Synthesis impurity

The chromatographic compound structures are referenced from Impurities.

TABLE 11 Chromatographic Characteristics of the Capillary Electrophoresis Stereoisomeric Purity Method

Compound	Relative migration time
Drug substance X	1.0
Impurity 1	1.2
Impurity 2	1.4

The chromatographic compound structures are referenced from Impurities.

TABLE 12 Operating Conditions of the Residual Solvent Gas Chromatography Method

Parameter	Conditions
Column	Silica column
Carrier gas	Nitrogen
Injector	Splitter
Detector	FID
Autosampler	Headspace

The operating conditions may be adapted in order to meet the system suitability requirements.

TABLE 13 Relative Elution Sequence of the Residual Solvent Chromatographic Method

Number	Organic volatile impurities
1	Methanol
2	Ethanol
3	Isopropanol

The analysis repeatability is tested with Drug Substance X and meets a RSD criterion that is $\leq$2.0% and at a concentration of 0.5 mg/mL with the related compounds and meets a RSD criterion that is $\leq$2.0%.

The intermediate precision is tested with Drug Substance X and meets a RSD criterion that is $\leq$2.0%.

Accuracy: The accuracy is tested by calculating the recovery at 0.5 mg/mL, which is between 95.0 and 105.0%.

Range: The analytical procedure has been demonstrated to be precise, accurate and linear in the range of 0.2 to 1.0 mg/mL for Drug Substance X and 0.002 to 0.02 mg/mL for the related compounds.

Detection Limit: The detection limit of 0.001 mg/mL has been calculated for Drug Substance X and related compounds.

Quantitation Limit: The quantitation limit is calculated for Drug Substance X and related compounds. The target value for the quantitation limit is $\leq$0.005 mg/mL.

Batch Analyses

For all phases of development, a minimum of 1 batch analysis is required.

Results of analyses for representative drug substance batches should be presented in tabular format.

Justification of Specification

Justification of specifications is typically unnecessary for development phases. During development, specifications will continue to be modified with the justification being finalized based upon the cumulative data of experience with the synthetic process and stability behavior of the drug substance. The following rationale is provided in the IMPD:

Since development of the active ingredient is under development, standard drug substance specifications to ensure identity, purity, and quality are in place. Well-developed drug substance specifications will be established as more experience with the drug substance is obtained and a justification of the specifications will be provided at that time.

In some instances, specifications may need to be justified. For example, in the case where the drug substance assay acceptance criteria are outside the normal range of 97.0–103.0 w/w. In this instance, a rationale should be provided that includes a discussion of the potential safety impact of the material.

REFERENCE STANDARDS OR MATERIALS

Typical text includes the following: Batch number 482395 is used as the chemical reference compound. Characterization of the drug substance batch 482395, which includes structural elucidation (MS, NMR, IR, UV, and elemental analysis) and routine control testing, was conducted. Details of this testing are provided in General Properties and Elucidation of Structure and Other Characteristics.

When the stock of this chemical reference compound becomes depleted, another lot of working standard will be used without notification to the authorities.

CONTAINER CLOSURE SYSTEM

The following description can be given: The container closure system for Drug Substance X consists of two antistatic low-density polyethylene (LDPE) bags, both sealed with a twist tie and placed in a fiberboard container with cap and band.

This container closure system is used in the drug substance stability studies as stated in the information provided in the Stability section of this submission.

STABILITY

1. Stability Summary and Conclusions

At the early stages of product development (i.e., Phase 1), only limited data may be available. In this case, only a summary and stability protocol (table indicating what tests at what time points) is provided. If data are available, no stability protocol needs to be submitted. Typically the first batches synthesized are put on stability. Additionally, drug substance batches manufactured according to a synthesis route that has undergone major changes are typically placed on stability. If data on material produced by a different synthetic route is the only data available, this data should be provided with an explanation of the origin of the data and justification that the stability data is representative of the current synthetic process.

1.1. Batches Tested

Insert a table which includes: batch number, synthesis method, manufacturing site, batch size, manufacturing date, packaging material, start of the stability study.

1.2. General Overview

Insert a table with study number and number of data reported per storage condition.

1.3. Stability Protocol

If data are available, no stability protocol is submitted. A reference is made to the stability data tables in Section S.7.3.

1.4. Conclusions

A brief summary of the drug substance stability is provided. The significance of the stability behavior of the drug substance with regard to storage and processing of drug product is included.

1.5. Re-Test Period and Storage Condition (Labeling)

A re-test period for the drug substance is given based upon the stability data available (Raphael, 2003). For drug substance that shows no instability at the specified storage conditions, a re-test period equivalent to 2 times the available real-time stability data available can be applied.

2. Stability Data

2.1. Test Procedures

A cross-reference to the analytical procedures in the section on Control of Drug Substance (Analytical Procedure) is made where many of these procedures are summarized. Additional analytical procedures are summarized here if not already included in Analytical Procedures.

2.2. Evaluation

A brief summary of the drug substance stability data and its significance is presented here for each test performed.

2.3. Overview of the Tabulated Stability Data

A tabular summary of the stability is presented.

CONCLUSION

The Clinical Trials Directive and the associated detailed guidances provide information on the format and content of the CMC section to be submitted for the support of clinical trials in Europe. This article described a regulatory approach with detailed guidance on specific sections for filing CMC information in the IMPD. The approach detailed the critical drug substance information necessary to support the investigation medicinal product dossier. The data presented should assure that the drug substance is under adequate control and provides for the safety of the clinical trial patient.

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