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# 4 Guideline on the Requirements for Quality Documentation 5 Concerning Biological Investigational Medicinal Products 6 in Clinical Trials

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# Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials

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# 1. Introduction (background)

## *1.1. Scope*

This guideline outlines the requirements for the data to be presented on the biological, chemical and pharmaceutical quality of Investigational Medicinal Products (IMP) containing biological / biotechnology derived substances.

In the EU, applications to conduct clinical trials are required to be submitted to the competent authority for approval prior to beginning a clinical trial in separately in each member state in which the trial is proposed to take place. Approval of trials is the responsibility of each involved Member State.

This guideline aims to ensure harmonised requirements for the documentation to be submitted throughout the European Community.

Available guidelines on the quality of biological / biotechnological medicinal products mainly address quality requirements for marketing authorisation applications. This guidance may not be fully applicable in the context of a clinical trial application; however the principles outlined in these guidelines are applicable and should be taken into consideration during development. A guideline on virus safety (EMEA/CHMP/BWP/398498/05) giving advice on the requirements for viral safety of IMP is available. The guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07, current version) is also relevant.

Assuring the quality of biological medicinal products is challenging, as often they consist of a number of product variants and process related impurities and it is difficult to predict the safety and efficacy profile of these variants and process related impurities. Unlike chemical entities, toxic impurities are generally not an issue, and the safety issues are more often related to the mechanism of action of the biological product or to immunogenicity.

In the context of an overall development strategy, normally several clinical trials, using products from different versions of the manufacturing process, will be initiated to generate data to support a Marketing Authorisation Application. The objective of this document is to address the quality requirements of an investigational medicinal product for a given clinical trial, not to provide guidance on a Company's overall development strategy for a medicinal product.

Nevertheless, for all clinical development phases, it is the responsibility of the applicant (sponsor) to ensure protection of the clinical trial subjects using a high quality IMP that is suitable for its intended purpose, and to appropriately address those quality attributes that may impair patient's safety (e.g. microbiological aspects, contamination, dose).

There are clear differences between the requirements for a dossier for a clinical trial and a marketing authorisation dossier. Whilst the latter has to ensure a consistent, state-of-the-art quality of a product for widespread use in patients, information to be provided for an IMP should mainly focus on those quality attributes related to safety aspects. The extent of the information required for an IMP Dossier (IMPD) should take into account the nature of the product, the state of development / clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself. When compiling the quality part of the IMPD for phase II and phase III clinical studies, the wider exposure of patients to the product and the progressive product knowledge have to be taken into account compared to phase I clinical studies. Based on the diversity of products to be used in the different phases of clinical trials, the requirements defined in this guideline can only be taken as illustrative and cannot be expected to present an exhaustive list. IMPs based on innovative and/or complex technologies may require a more detailed data package for assessment.

The documentation of the chemical and pharmaceutical quality of IMP containing biological substances should follow the Module 3 format of Common Technical Document, as described in ICH M4. Some of the explanatory text included in the ICH document is sufficiently general to address Marketing Authorisation Applications and IMPDs and the applicant should appropriately document these sections for the proposed clinical trial, in accordance with the data available at the time of submission. However, it is acknowledged that some specific sections are not adapted to the context of clinical trials, and thus this document will particularly focus on these points.

## *1.2. Scope of the Guideline*

This guideline addresses the documentation on the biological, chemical and pharmaceutical quality of IMPs containing biological / biotechnology derived substances to be submitted to the competent authority for approval prior to beginning a clinical trial in humans. It includes the requirements for IMPs to be tested in phase I, phase II and phase III studies.

The requirements defined in this guideline apply to recombinant proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates). These proteins and polypeptides can be highly purified and characterised using an appropriate set of analytical procedures. The principles that are outlined in the document may also apply to other biological products.

## *1.3. Legal Basis*

This guideline has to be read in conjunction with the introduction and general principles (4) and part I of the Annex I to Directive 2001/83/EC as amended.

Furthermore, the guideline is to be seen in connection with Directive 2001/20/EC[1] and the pertaining European Commission document “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” in its current version.

IMPs should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practices for Medicinal Products (GMP Directive 2003/94/EC and EudraLex Volume 4, The Rules Governing Medicinal Products in The European Community, Good manufacturing practice (GMP) Guidelines, with special emphasis on Annex 2 “Manufacture of Biological Medicinal Products for Human Use” and Annex 13 “Manufacture of Investigational Medicinal Products”).

## *1.4. General Points on Submission of Data for all IMPs*

The quality part of the IMPD should include comprehensive information related to the quality, manufacture and control of the IMP. It is preferable to present data in tabular form accompanied by a brief narrative highlighting the main points.

In certain situations, e.g. where the active substance from the specific source to be used for an IMP is already included in a medicinal product authorised within the EU, not all the documentation outlined in the following chapters needs to be submitted in the IMPD, but a simplified IMPD as described in the document “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” (current version) will suffice.

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 human use, which came into force on May 1, 2004

# 2. Information on the biological, chemical and pharmaceutical quality concerning biological investigational medicinal products in clinical trials

## *S Active Substance*

Reference to an Active Substance Master File or a Certificate of Suitability (CEP) of the European Directorate for the Quality of Medicines is neither acceptable nor applicable for biological/biotechnological active substances.

## *S.1. General Information*

### S.1.1. Nomenclature

Information concerning the nomenclature of the active substance (e.g. proposed INN-name, pharmacopoeial name, proprietary name, company code, other names or codes, if any) should be given.

### S1.2. Structure

The predicted structure, including higher order structure should be described. The schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be provided, as appropriate.

### S.1.3 General Properties

A list of physico-chemical and other relevant properties of the active substance should be provided including biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). The proposed mechanism of action should be described.

## *S.2. Manufacture*

### S.2.1. Manufacturer(s)

The name(s) and address(es) and responsibilities of each manufacturer, including contractors, and each proposed production site or facility involved in manufacture, testing and batch release should be provided.

### S.2.2. Description of Manufacturing Process and Process Controls

The manufacturing process and process controls should be adequately described. The manufacturing process typically starts with a vial(s) of the cell bank, includes cell culture, down-stream process (harvest(s), purification and modification reactions, filling), and storage and shipping conditions.

A flow chart of all successive steps and details of in-process-testing including appropriate acceptance criteria should be given. Critical steps and critical intermediates should be identified.

Batch(es) and scale definition should be provided, including information on any pooling of harvests or intermediates.

Any reprocessing undertaken during manufacture of the drug substance should be described and needs to be supported by data.

## S.2.3. Controls of Materials

*Raw and Starting Materials*

Materials used in the manufacture of the active substance (e.g. raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents) should be listed identifying where each material is used in the process. Information on the quality and control of these materials should be provided, as well as a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications). Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards appropriate for their intended use should be provided, as appropriate.

For all raw and starting materials of biological origin (including MCB generation), the source and the respective stage of the manufacturing process where the material is used should be indicated. Summaries of adventitious agents safety information for biologically-sourced materials should be provided in Appendix A.2.

*Source, History and Generation of the Cell Substrate*

A summarised description of the source and generation (flow chart of the successive steps) of the cell substrate, analysis of the expression vector used to genetically modify the cells and incorporated in the parental / host cell used to develop the Master Cell Bank, and the strategy by which the expression of the relevant gene is promoted and controlled in production should be provided, following the principles of CPMP/ICH Guidelines Q5B and Q5D.

Nucleic acid analysis of the expression construct including sequencing of the coding region should be performed prior to the initiation of clinical trials.

*Cell Bank System, Characterisation and Testing*

A Master Cell Bank (MCB) should be established prior to the initiation of Phase I trials. It is acknowledged that a Working Cell Bank (WCB) may not always be established.

Information on the generation, qualification and storage of the cell banks is required. The MCB and/or WCB should be characterised, appropriate specification should be set, and results of tests performed should be provided.

Cell banks should be characterised for relevant phenotypic and genotypic markers so that the identity, viability, and purity of cells used for the production are ensured. The generation and characterisation of the cell banks should be performed in accordance with principles of CPMP/ICH Guidelines Q5B and Q5D.

A summary of the safety assessment for adventitious agents and qualification of the cell banks used for the production of the active substance should be provided in A.2.

*Genetic stability*

Any available data on genetic stability including characterisation of End of Production Cells should be provided.

## S.2.4. Control of Critical Steps and Intermediates

Tests and acceptance criteria for the control of critical steps in the manufacturing process should be briefly summarised. If holding times are foreseen for process intermediates, periods and storage conditions should be justified and supported by data on physico-chemical, biological and microbiological characteristics/properties.

## S.2.5. Process Validation

Data on process validation should normally be collected throughout the development by the company, although they are not required to be submitted in the IMPD.

## S.2.6. Manufacturing Process Development

*Process improvement and comparability*

Manufacturing processes and their control strategies are continuously being improved and optimised, especially during development phase and early phases of clinical trials. These improvements and optimisations are considered as normal development work, and should be appropriately described in the submitted dossier. This description should allow a clear identification of the process versions used to produce each batch and the use of the batches in non-clinical and clinical trials, in order to establish an appropriate link between batches, pre- and post-process changes. The changes should be described and the rationale for these should be presented. Critical aspects and in-process controls should be highlighted and discussed. Comparative flow charts and/or list of process changes may be used. It is acknowledged that process modifications may require adaptation of in-process and release tests, and thus these tests and corresponding acceptance criteria should be reconsidered when changes are introduced.

The quality attributes of the active substance and relevant intermediates should be compared, using suitable analytical methods, which usually include routine tests that may be supplemented by additional characterisation tests (including stress studies), as appropriate. Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to assess the risk introduced by the change in terms of safety. The main purpose of these studies is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and will not raise any concern regarding the safety of the patients included in the clinical trial. Where the manufacturer's accumulated experience, and other relevant information and data are not sufficient to assess the risk introduced by the change, or if a potential risk to the patients is anticipated, a comparability exercise based only on quality considerations may not be sufficient.

In the case of first in human clinical trial, it is recommended to use investigational product derived from the same process as the one used in non-clinical studies. In the case where change(s) are introduced in the manufacturing process used to produce first in human clinical materials, an appropriate comparability exercise should be performed to ensure that the clinical material is representative of the non-clinical material, and that the difference(s) that may be detected are not anticipated to have a negative impact on the safety profile of the product when used in humans (see Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07)).

## *S.3. Characterisation*

## S.3.1. Elucidation of Structure and Other Characteristics

Characterisation of a biotechnological or biological substance (which includes the determination of physico-chemical properties, biological activity, immuno-chemical properties, purity and impurities) by appropriate orthogonal techniques is necessary to allow relevant specifications to be established. Reference to the literature data only is not acceptable. Adequate characterisation is performed in the development phase prior to phase I and, where necessary, following significant process changes. It is recognised that the extent of characterisation data will further increase in later phases.

Ultimately an extensive characterisation will also be required to support comparability of clinical batches used throughout development, and particularly those used in pivotal clinical trials, with the commercial lots to be produced for marketing authorisation.

For desired product and product-related substances, all relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications should be provided. Details should be provided on the biological activity (i.e. the specific ability or capacity of a product to achieve a defined biological effect). Prior to initiation of phase I studies, the biological activity should be determined using a relevant, reliable and qualified method.

The suitability of the methods employed should be justified.

### S.3.2. Impurities

Quantitative information on impurities should be provided as per ICH Q6B. Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables) and product related impurities (e.g. precursor, cleaved forms, degradation products, aggregates) should be addressed. In case only qualitative data are provided for certain impurities these should be justified.

The analytical methods used should be stated.

## *S.4. Control of the Active Substance*

During the clinical trial phases, where process validation data are incomplete, the quality attributes to control active substance and finished product are important to demonstrate pharmaceutical quality, product consistency and comparability after process changes. Therefore the quality attributes controlled throughout the development process should not be limited to the tests included in the specification for which preliminary acceptance criteria have been set.

Product characteristics that are not completely defined at a certain stage of development, or for which the available data is too limited to include it in the preliminary specification, should also be recorded for future evaluation. As a consequence, the results of product characteristics without preliminary acceptance criteria should be reported for information only (FIO).

### S.4.1. Specification

The specification for the batch(es) of active substance to be used in the clinical trial should define their acceptance criteria together with the used tests to exert sufficient control of the quality of the active substance. Tests for quantity, identity, purity and biological activity are mandatory. Upper limits, taking safety considerations into account, should be set for the impurities. The microbiological quality for active substances should be specified.

Because the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, they are by their nature inherently preliminary and may need to be reviewed and adjusted during further development.

*Additional information for phase III clinical trials*

As knowledge and experience increases, the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.

## S.4.2. Analytical Procedures

The analytical methods used for the active substance should be listed for all tests included in the specification (e.g. chromatographic methods, biological assay, etc.) including those tests reported FIO. A brief description for all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided.

For methods, which comply with a monograph of the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP, reference to the relevant monograph will be acceptable.

## S.4.3. Validation of Analytical Procedure

Validation of analytical procedures during clinical development is seen as an evolving process.

Analytical procedures, which are either described in Ph.Eur., the pharmacopoeia of a Member State, USP or JP general chapter, or are linked to a product specific monograph, are considered as validated.

For phase I clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form.

*Information for phase II and III clinical trials*

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

## S.4.4. Batch Analyses

As specifications are initially very wide, actual batch data are important for quality assessment. For quantitative parameters, actual numerical values should be presented.

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specifications) to be used in the given clinical trial. For early phase clinical trials, which are often characterised by a limited number of batches, results for all non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, for later phase clinical trials with a longer production history, it could be acceptable to have only a representative number of batches, if appropriately justified.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch should be identified.

## S.4.5. Justification of Specification(s)

A justification for the quality attributes included in the specification and the acceptance criteria for purity, impurities, biological activity and any other quality attributes which may be relevant to the performance of the finished product should be provided based on relevant development data, the lots used in non-clinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency and data from stability studies, as well as the methods used for their control. For impurities a justification that the product is safe for its intended use, considering the anticipated

exposure of volunteers and patients, respectively, will be required. Due to a too limited data base at an early stage of development (phase I/II) the acceptance criteria are not necessarily reflecting process capability. Based on the relevance of the potency assay criteria selected, the appropriate test (binding, cell based and/or animal assay) and specification should be justified. Correlation to *in-vivo* biological activity should be described.

Changes to a previously applied specification (e.g. addition or removal of parameters, widening of acceptance criteria) should be indicated and justified.

## *S.5. Reference Standards or Materials*

Due to the nature of biologically / biotechnology derived products a well characterised reference material is essential to ensure consistency between different batches of IMP but also to ensure the comparability of the product to be marketed with that used in clinical studies and to provide a link between process development and commercial manufacturing. The characterisation of the reference material should be performed with reliable state-of-the-art analytical methods, which should be sufficiently described. Information regarding the manufacturing process used to establish the reference material should be provided.

If available an international or Ph.Eur. standard should be used as primary reference material. However it should be noted that the use of an international or Ph.Eur. standard might be limited to certain defined test methods, e.g. biological activity.

## *S.6. Container Closure System*

The immediate packaging material used for the active substance should be stated.

## *S.7. Stability*

### S.7.1. Stability Protocol / Material and Method

A suitable stability protocol covering the proposed storage period of the active substance including all necessary information should be provided, including, specifications, analytical methods and test intervals. The testing interval should normally follow ICH Q5C.

The quality of the batches of active substance placed into the stability program should be representative of the quality of the material to be used in the planned clinical trial.

The active substance entered into the stability program should be stored in containers that use the same type and materials of container closure system that is used for active substance used to manufacture the clinical trial batch.

Studies should evaluate active substance stability under the proposed storage conditions. Accelerated and stress condition studies are recommended as they may help understanding the degradation profile of the product and support extension of shelf-life.

Stability-indicating methods should be included in this stability protocol to provide assurance that changes in the purity / impurity profile and potency of the active substance would be detected. Even if it has not yet been proven to be stability-indicating, a potency assay should be included in the protocol. Shelf-life specification and limits should be derived from all available information.

The re-test period (as defined in ICH Q1A guideline) is not applicable to biological / biotechnology derived active substances.

## S.7.2. Stability Data / Results

Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. Stability data of relevant development batches or batches manufactured using previous manufacturing processes should be provided as well but they are to be used as supportive data.

The relevant stability data available should be summarised in tabular format, specifying the batches tested, date of manufacture, process version, formulation(s), time-points, test methods, acceptance criteria and results.

For quantitative parameters, actual numerical values should be presented. Any observed data trends should be discussed.

Progressive requirements will need to be applied to reflect the amount of available data and emerging knowledge about the stability of the active substance during the different phases of clinical development. For phase III the applicant should have a comprehensive understanding of the stability profile of the active substance.

## S.7.3. Shelf-life Determination

The claimed shelf-life of the active substance under the proposed storage conditions should be stated and accompanied by an evaluation of the available data. Any observed trends should be discussed.

The requested storage period should be based on long term, real time and real-condition stability studies, as described in ICH Q5C. However, extension of the shelf-life beyond the period covered by real-time stability data may be acceptable, if supported and justified by relevant data, including accelerated stability studies.

The maximum extension should not exceed two-fold and should not be more than twelve months beyond the provided stability data obtained with representative batch(es). However, extension beyond the intended duration of the long term studies is not acceptable.

Prior knowledge including platform technologies should be taken into consideration when designing a stability protocol; however, this data may not be sufficient to justify the shelf-life of the actual IMP.

## S.7.4. Commitment

Where an extension of the shelf-life is claimed, the Applicant should commit to perform the proposed stability program according to the presented protocol, and, in the event of unexpected issues, to inform Competent Authorities of the situation, including any corrective action proposed.

## S.7.5 Post-approval Extension

Further shelf-life extension based on the agreed protocol would not be considered as substantial amendments if:

- the additional extension does not exceed two-fold of the approved shelf-life, and is not more than twelve months
- the extension is covered and in compliance with the approved stability protocol
- no significant trend or out-of-specification results (OoS) has been detected in ongoing stability studies

- the Applicant commits to inform Competent Authorities of unexpected stability issues in the ongoing study (including trends and OoS) and to propose corrective action as appropriate

**Any extension of the shelf-life outside the agreed protocol or without prior commitment is considered a substantial amendment.**

## *P Investigational Medicinal Product Under Test*

### *P.1. Description and Composition of the Investigational Medicinal Product*

The qualitative and quantitative composition of the IMP should be stated. A description of the finished product and its composition should be provided. The information provided should include:

- a short statement or a tabulation of the dosage form
- composition, i.e. list of all components of the dosage form and their amount on a per-unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications)
- description of accompanying solvents(s)
- type of container and closure used for the dosage form and accompanying reconstitution diluent, if applicable.

### *P.2. Pharmaceutical Development*

For early development there may be only limited information to include in this section.

A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

For product requiring additional preparation of the finished product (e.g. reconstitution, dilution, mixing), the compatibility with the used materials (e.g. solvents, diluents, matrix) should be demonstrated and the method of preparation should be summarised (reference may be made to a full description in the clinical protocol).

It should be documented that the combination of intended formulation and packaging material does not impair correct dosing, ensuring for example that the product is not adsorbed to the wall of the container or infusion system. This is particularly relevant for low dose and highly diluted presentations.

Where applicable, the reliable administration of very small doses in First-in-human studies should be addressed as laid down in the Guideline on Strategies to Identify and Mitigate Risks for First-in-human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07).

#### P.2.1 Manufacturing Process Development

Changes in the manufacturing process including changes in formulation and dosage form compared to previous clinical trials should be described. Even if a full comparability exercise as described in ICH Q5E cannot be provided, the changes in the manufacturing process should be supported by analytical data and batch results of the batches before and after the changes. These data should be sufficiently detailed to allow an appropriate understanding of the changes and assessment of possible consequences to the safety of the patient.

Any changes in the formulation during the clinical phases should be documented and justified with respect to their impact on quality, safety, clinical properties, dosing and stability of the finished product.

## *P.3. Manufacture*

### P.3.1. Manufacture(s)

The name(s), address(es) and responsibilities of all manufacturer(s) for each proposed production site involved in manufacture and testing should be provided. In case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

### P.3.2. Batch Formula

The batch formula for the batch(es) to be used for the clinical trial should be presented. This should include a list of all components to be used including a reference to their quality standards. The batch sizes or range of batch sizes should be given.

### P.3.3. Description of Manufacturing Process and Process Controls

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

Most of the finished products containing recombinant proteins and monoclonal antibodies are manufactured by an aseptic process, which is considered to be non-standard. Non-standard manufacturing processes or new technologies and new packaging processes should be described in detail (see Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03)).

### P.3.4. Control of Critical Steps and Intermediates

Tests and acceptance criteria for the control of critical steps in the manufacturing process should be briefly summarised.

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.

It is essential for product quality and safety to ensure that the highest level of sterility assurance is achieved in conjunction with the lowest level appropriate of pre-sterilisation bioburden.

For aseptic manufacturing processes, the bioburden before sterile filtration should be specified as described in the Note for Guidance on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95). Due to limited availability of the formulated Finished Product, a pre-/filtration volume of less than 100 ml might be tested if justified.

Reprocessing may be acceptable for particular manufacturing steps (e.g. re-filtration) only if the steps are adequately described and appropriately justified.

### P.3.5. Process Validation and/or Evaluation

The validation of the aseptic manufacturing process and/or lyophilisation should be briefly described. 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, i.e. on bioburden and media fill runs.

## *P.4. Control of Excipients*

### P.4.1. Specification

References to the Ph.Eur., the pharmacopoeia of an EU Member State, USP or JP may be applied. For excipients not covered by any of the aforementioned standards, an in-house specification should be provided.

### P.4.2. Analytical Procedures

In cases where reference to a pharmacopoeial monograph listed under P.4.1 cannot be made, the analytical methods used should be indicated.

### P.4.3. Validation of the Analytical Procedures

Not applicable.

### P.4.4. Justification of Specifications

For non-compendial excipients as listed above in P.4.1, the in-house specification should be justified.

### P.4.5. Excipients of Animal or Human Origin

For excipients of human or animal origin, information should be provided regarding adventitious agents safety evaluation (e.g. sources, specifications, description of the testing performed) and viral safety data according to Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/05) in Appendix A.2.

If human albumin or any other plasma derived medicinal product is used as an excipient, information regarding adventitious agents safety evaluation should follow the relevant chapters of the Guideline on Plasma-Derived Medicinal Products (CPMP/BWP/269/95, current version). If the plasma derived component has already been used in a product with a MA then reference to this can be made.

### P.4.6. Novel Excipients

For excipient(s) used for the first time in a finished product or by a new route of administration, full details of manufacture, characterisation and controls, with cross references to supporting safety data (non-clinical and/or clinical), should be provided according to the active substance format (details in A.3).

## *P.5. Control of the Investigational Medicinal Product*

### P.5.1. Specification

The same principles as described for setting the active substance specification should be applied for the finished product. In the specification, the tests used as well as their acceptance criteria should be defined for the batch(es) of finished product to be used in the clinical trial to enable sufficient control of quality of the finished product. Tests for content, identity, purity and biological activity, sterility and endotoxin are mandatory where applicable. Upper limits, taking safety considerations into account,

should be set for the impurities. They may need to be reviewed and adjusted during further development.

Acceptance criteria for finished product quality attributes should take into account safety considerations and the stage of development. Since the acceptance criteria are normally based on a limited number of development batches and batches used in non-clinical and clinical studies, their nature is inherently preliminary. They may need to be reviewed and adjusted during further development.

The analytical methods and the limits for content and bioactivity should ensure a correct and safe starting dose.

For the impurities not covered by the active substance specification, upper limits should be set, taking safety considerations into account.

*Additional information for phase III clinical trials*

As knowledge and experience increases the addition or removal of parameters and modification of analytical methods may be necessary. Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed for phase III clinical trials and, where appropriate, adjusted to the current stage of development.

## P.5.2. Analytical Procedures

The analytical methods should be described for all tests included in the specification. For some proteins and complex or innovative pharmaceutical forms, a higher level of detail may be required.

For further requirements refer to S.4.2.

## P.5.3. Validation of Analytical Procedures

For requirements refer to S.4.3.

## P.5.4. Batch Analysis

The focus of this section is to demonstrate the quality of the batches (conformance to established preliminary specification) to be used in the given clinical trial. For early phase clinical trials, which are often characterised by a limited number of batches, results for all non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, for advanced phase clinical trials with a longer production history, it could be acceptable to have only a representative number of batches, if appropriately justified. As specifications are initially very wide, actual batch data are important for quality assessment.

Batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed together with the use of the batches. The manufacturing process used for each batch should be identified.

## P.5.5. Characterisation of Impurities

Additional impurities and degradation products observed in the IMP, but not covered by section S.3.2, should be identified and quantified as necessary.

### P.5.6. Justification of Specifications

A justification for the quality attributes included in the drug product specification should be provided mainly based on the drug substance specification. Stability indicating quality attributes should be considered. The acceptance criteria for content, purity, impurities and degradation products, biological activity, endotoxin, sterility and any other attribute relevant to the quality and safety of the finished product should be justified.

### *P.6. Reference Standards or Materials*

The parameters for characterisation of the reference standard should be submitted, where applicable.

Section S.5 - Reference Standards or Materials - may be referred to, where applicable.

### *P.7. Container Closure System*

The intended immediate packaging and additionally, where relevant for the quality of the finished product, the outer 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. If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. If applicable, a CE mark for an additional medical device should be confirmed.

For parenterals having a potential for interaction between product and container closure system more details may be needed.

### *P.8. Stability*

The same requirements as for the active substance are applied to the finished product, including the stability protocol, stability results, shelf-life determination, stability commitment and post-approval extension. Stability studies should provide sufficient assurance that the IMP will be stable during its intended storage period. The presented data should justify the proposed shelf life of the product from its release to its administration to patients. The stability protocol for the finished product should take into account the knowledge acquired on the stability profile of the active substance.

Bracketing and matrixing approaches may be acceptable, where justified.

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.

## 3. Information on the Chemical and Pharmaceutical Quality of Authorised, Non-modified Test and Comparator Products in Clinical Trials

For test and comparator products to be used in clinical trials which have already been authorised in the EU/EEA, in one of the ICH-regions or one of the Mutual Recognition Agreement (MRA) partner countries, it will be sufficient to provide the Summary of Product Characteristics (SmPC), the name of the Marketing Authorisation Holder (MAH) and the MA number as proof for the existence of a MA. For repackaged comparator products, see 4.3.

For authorised products sourced from those countries outside the EU/EEA mentioned in the first paragraph, information on the analytical methods needed for at least reduced testing (e.g. identity)

should be provided. The relevant analyses, tests or checks necessary to confirm quality as required by Article 13 3(c) of Directive 2001/20/EC shall therefore be based on proof of existence of the equivalent of a Marketing Authorisation, combined with confirmation of identity.

The applicant or sponsor of the clinical trial has to ensure that the IMP is stable at least for the anticipated duration of the clinical trial in which it will be used. For authorised products, it will be sufficient to state the respective expiry date assigned by the manufacturer.

For IMPs sourced from outside of the EU/EEA, MRA-partner countries or ICH regions, a full documentation should be submitted.

# 4. Information on the Clinical and Pharmaceutical Quality of Authorised, Modified Comparator Products in Clinical Trials

In preparing supplies for clinical trials, applicants often modify or process medicinal products which have already been authorised in order to use them as comparator products in blinded studies.

As the MAH of a comparator product is only responsible for the unchanged product in its designated and authorised packaging, there is a need to ensure that the quality of the product is not negatively affected by the modifications performed by the applicant or sponsor of the clinical trial, with special emphasis on the biopharmaceutical properties. For details see Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products (CHMP/QWP/185401/2004 final).

# 5. Information on the Chemical and Pharmaceutical Quality Concerning Placebo Products in Clinical Trials

The quality documentation to be submitted for placebos is limited to the sections of the product part. For details see Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products (CHMP/QWP/185401/2004 final).

# 6. Appendices

## *A.1. Facilities and Equipment*

All manufacturing and testing sites should be listed. Premises and equipment have to be qualified (Annex 13 EU GMP Nr. 17). GMP compliance has to be confirmed (Reference to Dir. 2001/20).

## *A.2. Adventitious Agents Safety Evaluation*

All materials of human or animal origin used in the manufacturing process of both active substance and finished product, or such materials coming into contact with active substance or finished product during the manufacturing process, should be identified. Information assessing the risk with respect to potential contamination with adventitious agents of human or animal origin should be provided in this section.

*TSE agents*

Detailed information should be provided on the avoidance and control of transmissible spongiform encephalopathy agents. This information can include, for example, certification and control of the production process, as appropriate for the material, process and agent.

The Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01) in its current version is to be applied.

*Viral safety*

Where applicable, information assessing the risk with respect to potential viral contamination should be provided in this section. The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated. The documentation should comply with the requirements as outlined in the Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/05).

*Other adventitious agents*

Detailed information regarding other adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the core dossier.

### *A.3. Novel Excipients*

For novel excipients, information as indicated in section S of the CTD should be provided in line with the respective clinical phase.

### *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.

## 7. Changes to the Investigational Medicinal Product with a Need to Request a Substantial Amendment to the IMPD

Article 10(a) of the Directive 2001/20/EC allows amendments to be made to the conduct of a clinical trial after its commencement. It does not require notification of non-substantial amendments; only amendments that are substantial must be notified to the CA and ethics committee concerned.

As per EudraLex Vol. 10 (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), amendments to the trial are regarded as “substantial” where they are likely to have a significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any IMP used in the trial.

In all cases, an amendment is only to be regarded as “substantial” when one or more of the above criteria are met.

In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions. Guidance given in this section relates only to changes that need to be notified to the competent authorities.

The documentation submitted for a substantial amendment should be sufficiently detailed to allow an assessment of the impact of the change. In addition, a summary / list of changes to the original IMPD should be provided.

The following examples of changes to IMP quality data are always to be regarded as “substantial”:

- manufacturer(s) of active substance or finished product
- substantial changes in the manufacturing process (such as new expression cell line, addition or omission of a purification step, changes of steps affecting viral clearance, any reprocessing not described in the IMPD)
- changes leading to the occurrence of new impurities and product related substances
- change in specification, if acceptance criteria are widened or test procedures are deleted or replaced
- change to the formulation including changes in active substance concentration and excipient composition
- immediate packaging material, if the nature of material is changed
- shelf-life extension that goes beyond the accepted stability protocol
- changes in the approved in-use stability recommendations.

Assessment of an IMP should be focused on patient safety. Therefore, any amendment involving a potential new risk has to be considered a “substantial” amendment.

# References


Eudralex - The Rules Governing Medicinal Products in the European Community:

- Volume 2B - Notice to applicants, Medicinal products for human use, Presentation and format of the dossier, Common Technical Document (CTD)
- Volume 4 - Good manufacturing practice (GMP) Guidelines, with special emphasis on Annex 2 “Manufacture of Biological Medicinal Products for Human Use” and Annex 13 “Manufacture of Investigational Medicinal Products”
- Volume 10 - Clinical Trials Guidelines, 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

Directives:

- Directive 2003/94/EC, laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Directive 2001/20/EC, 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 human use
- Directive 2001/83/EC, on the Community code relating to medicinal products for human use

Guidelines:

- Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/05)
- Guideline on Strategies to Identify and Mitigate Risks for First-in-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07)
- Guideline on Plasma-Derived Medicinal Products (CPMP/BWP/269/95)
- Guideline on the Requirements to the Chemical and Pharmaceutical Quality Documentation Concerning Investigational Medicinal Products in Clinical Trials (CHMP/QWP/185401/2004)
- Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03)
- Note for Guidance on Manufacture of the Finished Dosage Form (CPMP/QWP/486/95)
- Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products (EMEA/410/01)
- CPMP/ICH Guideline Q1A: Stability Testing of New Drug Substances and Products
- CPMP/ICH Guideline Q5B: Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products
- CPMP/ICH Guideline Q5C: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products
- CPMP/ICH Guideline Q5D: Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products
- CPMP/ICH Guideline Q6B: Specifications : Test Procedures and Acceptance Criteria for Biotechnological/Biological Products

All referenced documents should be used in their current versions.