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Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials

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Table of contents

1. Introduction (background)

The "Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial"[1] ('detailed guidance CT-1') sets out the requirements as regards data related to an investigational medicinal product (IMP) to be submitted with the request for a clinical trial authorisation in the IMP Dossier (IMPD).

This guideline addresses the specific documentation requirements on the biological, chemical and pharmaceutical quality of IMP containing biological / biotechnology derived substances in cases where no 'simplified IMPD' is submitted (see section 2.7.3. of the detailed guidance CT-1).

Moreover, this guideline lists, as regards documentation on the biological, chemical and pharmaceutical quality of the IMP, examples of amendments which are typically considered as 'substantial' (see section 3 of the detailed guidance CT-1).

The guidance outlined in this document applies to proteins and polypeptides, their derivatives, and products of which they are components (e.g. conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell-culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures.

The principles may also apply to other product types such as proteins and polypeptides isolated from tissues and body fluids.

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.

S.1.2. Structure

A brief description of the predicted structure should be provided. Higher order structure, schematic amino acid sequence indicating glycosylation sites or other post-translational modifications and relative molecular mass should be included, as appropriate.

[1] OJ C82, 30.3.2010, p. 1.

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 discussed.

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 and includes cell culture, harvest(s), purification, modification reactions and filling. Storage and shipping conditions should be outlined.

A flow chart of all successive steps including in-process-testing should be given. The results of in-process testing may be recorded as action limits or reported as preliminary acceptance criteria. During development, as process knowledge is gained, further detail of in-process testing and the criteria should be provided and acceptance criteria reviewed.

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

Any reprocessing during manufacture of the active substance (e.g. filter integrity test failure) should be described and justified.

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. Reference to quality standards (e.g. compendial monographs or manufacturer's in-house specifications) should be made. Information on the quality and control of non-compendial materials should be provided. Information demonstrating that materials (including biologically-sourced materials, e.g. media components, monoclonal antibodies, enzymes) meet standards applicable for their intended use should be provided, as appropriate.

For all raw materials of biological origin (including those used in the cell bank 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 (MCB), 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 guideline Q5D.

Cell bank system, characterisation and testing

A 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 and results of tests performed should be provided. The generation and characterisation of the cell banks should be performed in accordance with principles of CPMP/ICH guideline Q5D.

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.

Nucleic acid sequence of the expression cassette including sequence of the coding region should be confirmed prior to the initiation of clinical trials.

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, if needed.

Cell substrate stability

Any available data on cell substrate stability 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 provided. It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.

Hold times and storage conditions for process intermediates should be justified and supported by data, as appropriate.

S.2.5. Process validation and /or evaluation

Process validation / evaluation data should be collected throughout the development, although they are not required to be submitted in the IMPD.

For manufacturing steps intended to remove or inactivate viral contaminants, the relevant information should be provided in the section A2, Adventitious agents safety evaluation.

S.2.6. Manufacturing process development

Process improvement

Manufacturing processes and their control strategies are continuously being improved and optimised, especially during the 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. Changes to the manufacturing process and controls should be summarized and the rationale for changes should be presented. This description should allow a clear identification of the process versions used to produce each batch used in non-clinical and clinical studies, in order to establish an appropriate link between pre-change and post-change batches. Comparative flow charts and/or list of process changes may be used to present the process evolution. 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.

Comparability exercise

Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to ensure that the change would not have an adverse impact on clinical characteristics of the product. The main purpose of this exercise is to provide assurance that the post-change product is suitable for the forthcoming clinical trials and that it will not raise any concern regarding safety of the patients included in the clinical trial.

This comparability exercise should normally follow a stepwise approach, including comparison of quality attributes of the active substance and relevant intermediates, using suitable analytical methods. Analytical methods usually include routine tests, and may be supplemented by additional characterisation tests (including orthogonal methods), as appropriate. Where the manufacturer's accumulated experience and other relevant information 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.

During early phases of non-clinical and clinical studies, comparability testing is generally not as extensive as for an approved product. In the case of first in human clinical trial, it is recommended to use investigational product representative of the material used in non-clinical studies (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 techniques is necessary to allow relevant specification 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.

For the desired product 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). Usually prior to initiation of phase I studies, the biological activity should be determined using a relevant, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will further increase in later phases.

The rationale for selection of the methods used for characterisation should be provided and their suitability should be justified.

S.3.2. Impurities

Process related impurities (e.g. host cell proteins, host cell DNA, media residues, column leachables) and product related impurities (e.g. precursors, cleaved forms, degradation products, aggregates) should be addressed. Quantitative information on impurities should be provided including maximum amount for the highest clinical dose. For certain process-related impurities (e.g. antifoam agents), an estimation of clearance may be justified.

In case only qualitative data are provided for certain impurities, this should be justified.

S.4. Control of the active substance

During the clinical trial phases, where process validation data are incomplete, the quality attributes to control the active substance 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.

S.4.1. Specification

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

As 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.

Product characteristics that are not completely defined at a certain stage of development, or for which the available data is too limited to establish relevant acceptance criteria, should also be recorded. As a consequence, such product characteristics could be included in the specification, without pre-defined acceptance limits. The results should be reported in the Batch Analyses section (S.4.4).

Additional information for phase II and 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 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 without acceptance limits. 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 normally 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 specification may be 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 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 relevant non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, with longer production history, it could be acceptable to provide results for only a number of representative 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

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 medicinal product should be provided. The justification should be based on relevant development data, the batches used in non-clinical and/or clinical studies and data from stability studies, taking into account the methods used for their control. It is acknowledged that during early clinical development, the acceptance criteria may be wider and may not reflect process capability. Wider limits may be set at phase I/II when there is only limited experience. However, for those quality attributes that may impact patient safety, the limits should be carefully considered taking into account available knowledge (e.g. process capability, product type, dose, duration of dosing etc). The relevance of the selected potency assay and its proposed acceptance limits should be justified.

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 more than one reference standard has been used during the clinical development, a qualification history should be provided describing how the relationship between the different standards was maintained.

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. If an international or Ph.Eur. standard is not available, an in-house reference material should be established.

S.6. Container closure system

The immediate packaging material used for the active substance should be stated. Possible interaction between the active substance and the immediate packaging should be considered.

S.7. Stability

Stability summary and conclusions (protocol / material and method)

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

The quality of the batches of the 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 the active substance used to

manufacture the clinical trial batch. Containers of reduced size are usually acceptable for the active substance stability testing.

Studies should evaluate the 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. A potency assay should be included in the protocol, unless otherwise justified.

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

Stability data / results

Stability data should be presented for at least one batch representative of the manufacturing process of the clinical trial material. In addition, stability data of relevant development batches or batches manufactured using previous manufacturing processes could be provided. Such batch data may be used in the assignment of shelf life for the active substance provided appropriate justification of representative quality for the clinical trial material is given.

The relevant stability data available should be summarised in tabular format, specifying the batches tested, date of manufacture, process version, composition, storage conditions, 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.

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 temperature 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 shelf-life after the 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 stability studies is not acceptable.

Prior knowledge including platform technologies could be taken into consideration when designing a stability protocol; however, on its own this data is not considered sufficient to justify the shelf-life of the actual IMP.

Where extensions of the shelf-life are planned, 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.

On shelf life extension by way of substantial amendment, see section 4.

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. 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 diluents(s)
- a brief description of the 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 products requiring additional preparation of the medicinal 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).

Manufacturing process development

Changes in the manufacturing process including changes in formulation and dosage form compared to previous clinical trials should be described. An appropriate comparability exercise should support significant changes, e.g. formulation changes. In this regard, expectations are similar to those described in S.2.6. This 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 medicinal product.

P.3. Manufacture

P.3.1. Manufacturer(s)

The name(s), address(es) and responsibilities of all manufacturer(s) for each proposed production site involved in manufacture, testing and batch release 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. The batch sizes or range of batch sizes should be given.

P.3.3. Description of manufacturing process and process controls

A flow chart of all successive steps including in-process-testing should be given. The results of in-process testing may be recorded as action limits or reported as preliminary acceptance criteria. During development, as process knowledge is gained, further detail of in-process testing and the criteria should be provided and acceptance criteria reviewed.

Most of the 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 sufficient detail (see the 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 provided. It is acknowledged that due to limited data at an early stage of development (phase I/II) complete information may not be available.

If holding times are foreseen for process intermediates, periods and storage conditions should be provided and justified by data in terms of physicochemical, biological and microbiological properties.

For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable, depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, it is necessary to use a pre-filtration through a bacteria-retaining filter to obtain a sufficiently low bioburden. Due to limited availability of the formulated medicinal product, a pre-/filtration volume of less than 100 ml may 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 state of validation of the aseptic processing and lyophilisation should be briefly described, if applicable. Taking into account EudraLex Vol. 4, Annex 13, the validation of sterilising processes should be the same standard as for product authorised for marketing. The dossier should particularly include information directly regarding the product safety, 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 specification

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

P.4.5. Excipients of human or animal 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 the Guideline on Virus Safety Evaluation of Biotechnological Investigational Medicinal Products (EMEA/CHMP/BWP/398498/05) in Appendix A.2. Furthermore, compliance with the TSE guideline (EMA/410/01, current version) should be documented in section 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). 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 medicinal 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 medicinal product. In the specification, the tests used as well as their acceptance criteria should be defined for the batch(es) of the product to be used in the clinical trial to enable sufficient control of quality of the product. Tests for contents, identity and purity are mandatory. Tests for sterility and endotoxin are mandatory for sterile products. A test for biological activity should be included unless otherwise justified. 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 medicinal 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 dosing.

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

Additional information for phase II and III clinical trials

As knowledge and experience increases the addition or removal of parameters and modification of analytical methods may be necessary. Specification and acceptance criteria set for previous 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

As specification may be 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 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 relevant non-clinical and clinical batches should be provided, including the results of batches to be used in the given clinical trial. However, with

longer production history, it could be acceptable to provide results for only a number of representative 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.

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 specification

A justification for the quality attributes included in the product specification should be provided mainly based on the active substance specification. Stability indicating quality attributes should be considered. The proposed acceptance criteria 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 primary packaging to be used for the IMP in the clinical trial should be described. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, description and specifications should be provided. If applicable, the 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 medicinal product, including the stability protocol, stability results, shelf-life determination, including extension of shelf-life beyond the period covered by real-time stability data, 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 IMP 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. Appendices

A.1. Facilities and equipment

Not applicable.

A.2. Adventitious agents safety evaluation

All materials of human or animal origin used in the manufacturing process of both the active substance and the medicinal product, or such materials coming into contact with active substance or medicinal 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 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. 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.

4. Substantial amendments

The following is a non-exhaustive list of amendments that are typically 'substantial' (see section 3 of the detailed guidance CT-1 for more details):

- manufacturer(s) of the active substance or the medicinal 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 the 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.
- any extension of the shelf-life outside the agreed protocol or without prior commitment (see section S.7 and P.8).

However, shelf-life extension based on the agreed protocol is typically not considered as substantial amendment if:

- each additional extension of the shelf-life 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 trends or out-of-specification results (OoS) have been detected in ongoing stability studies at the designated storage temperature
- 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