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

Draft

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Comments should be provided using this template. The completed comments form should be sent to BWPsecretariat@ema.europa.eu

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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. Objectives of the guideline

The following guideline is to be seen in connection with Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, which came into force on June 20, 2014

Since clinical trials can be designed as multi-centre studies potentially involving different Member States, it is the aim of this guideline to define harmonised requirements for the documentation to be submitted throughout the European Union.

Most available guidelines on the quality of biological / biotechnological medicinal products address quality requirements for marketing authorisation applications. Whilst these guidelines may not be fully applicable in the context of a clinical trial application, the principles outlined are applicable and should be taken into consideration during product development. The guidelines on Virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) and Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) should also be consulted.

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

In the context of an overall development strategy, several clinical trials, using products from different versions of the manufacturing process, may 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 and 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 investigational medicinal product (IMP) that is suitable for its intended purpose, and to appropriately address those quality attributes that may impair patients' safety (e.g. microbiological aspects, viral contamination, dose).

Due to 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 are not presented as an exhaustive list. IMPs based on innovative and/or complex technologies may require a more detailed data package for assessment.

1.2. Scope

This guideline addresses the specific documentation requirements on the biological, chemical and pharmaceutical quality of IMPs containing biological / biotechnology derived substances.

Moreover, this guideline lists, as regards documentation on the biological, chemical and pharmaceutical quality of the IMP, examples of modifications which are typically considered as 'substantial'.

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 guideline also applies to Auxiliary Medicinal Products containing these proteins and polypeptides as active substances. The requirements depend on the type of the product (authorised / not authorised / modified / non-modified medicinal product).

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

Advanced Therapy Medicinal Products are excluded from this guideline.

1.3. General points concerning all IMPs

IMPs should be produced in accordance with the principles and the detailed guidelines of good manufacturing practices for medicinal products (The rules governing medicinal products in the European Community, Volume IV).

1.4. Submission of data

The investigational medicinal product dossier (IMPD) should be provided in a clearly structured format following the CTD format of Module 3 and include the most up-to-date available information relevant to the clinical trial at time of submission of the clinical trial application.

If the active substance used is already authorised in a finished product within the EU/EEA or in one of the ICH regions reference can be made to the valid marketing authorisation. However, depending on the nature of the product additional information might be necessary. A statement should be provided that the active substance has the same quality as in the approved product.

The name of the finished product, the marketing authorisation number or its equivalent, the marketing authorisation holder and the country that granted the marketing authorisation should be given. (Reference is made to Table 1 of Regulation 536/2014)

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. recommended International Non-Proprietary Name (INN), 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.

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 one or more vials 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 relevant process parameters and in-process-testing should be given. The control strategy should focus on safety relevant in-process controls (IPCs) and acceptance criteria for critical steps (e.g. ranges for process parameters of steps involved in virus removal) should be established for manufacture of phase I/II material. These in-process controls (process parameters and in process testing as defined in ICH Q11) should be provided with action limits or preliminary acceptance criteria. For other IPCs, monitoring might be appropriate and acceptance criteria or action limits do not need to be provided. Since early development control limits are normally based on a limited number of development batches, they are inherently preliminary. During development, as additional process knowledge is gained, further details of IPCs 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. Reprocessing could be considered in exceptional circumstances. For biological products, these situations are usually restricted to certain re-filtration and re-concentration steps upon technical failure of equipment or mechanical breakdown of a chromatography column.

S.2.3. Control 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 manufacturers' 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 human or animal 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 safety information on adventitious agents for these materials should be provided in Appendix A.2.

Source, history and generation of the cell substrate

A brief 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 ICH 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 if used should be characterised and results of tests performed should be provided. Clonality of the cell banks should be addressed for mammalian cell lines. The generation and characterisation of the cell banks should be performed in accordance with the principles of ICH 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.

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

As for any process change, the introduction of a WCB may potentially impact the quality profile of the active substance and comparability should be considered (see section S.2.6. Manufacturing process development).

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 appropriate.

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. Cross reference to section S 2.2 might be acceptable for acceptance criteria or action limits. 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, if relevant.

S.2.5. Process validation

Process validation data should be collected throughout 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. Changes to the manufacturing process and controls should be summarized. 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. If process changes are made to steps involved in viral clearance, justification should be provided as to whether a new viral clearance study is required, or whether the previous study is still applicable.

Comparability exercise

Depending on the consequences of the change introduced and the stage of development, a comparability exercise may be necessary to demonstrate that the change would not adversely impact the quality of the active substance. In early phases 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. In addition, for later phases, it should be assessed if the post-change material could impact the efficacy of the IMP.

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 manufacturers' 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 trials, an IMP representative of the material used in non-clinical studies should be used (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 a suitable specification to be established. Reference to literature data only is not acceptable, unless otherwise justified by prior knowledge from similar molecules for modifications where there is no safety concern (e.g. C-terminal lysine for monoclonal antibodies). Adequate characterisation should be performed in the development phase prior to phase I and, where necessary, following significant process changes.

All relevant information available on the primary, secondary and higher-order structure including post-translational (e.g. glycoforms) and other modifications of the active substance 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 an appropriate, reliable and qualified method. Lack of such an assay should be justified. It is recognised that the extent of characterisation data will increase during development.

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

When process validation data are incomplete, the quality attributes used 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 active substance to be used in the clinical trial should define acceptance criteria together with the tests used to exert sufficient control of the quality of the active substance. Tests and defined acceptance criteria are mandatory for quantity, identity and purity and a limit of 'record' or 'report results' will not be acceptable for these quality attributes. A test for biological activity should be included unless otherwise justified. Upper limits, taking into account safety considerations , 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 (e.g. glycosylation, charge heterogeneity) 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. In such cases, a limit of 'record' or 'report results' is acceptable. The results should be reported in the Batch Analyses section (S.4.4).

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 trials should be reviewed and, where appropriate, adjusted to the current stage of development.

S.4.2. Analytical procedures

The analytical methods used for all tests included in the active substance specification (e.g. chromatographic methods, biological assay, etc.) should be listed including those tests reported without acceptance limits. A brief description of all non-compendial analytical procedures, i.e. the way of performing the analysis, should be provided, highlighting controls used in the analysis.

For methods which comply with a monograph of the European Pharmacopoeia (Ph. Eur.), the pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP), reference to the relevant monograph will be acceptable.

S.4.3. Validation of analytical procedures

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, or are linked to a product specific monograph, are normally considered as validated. Proposed modifications or alternatives to compendial methods must be validated

For phase I and II 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. If validation studies have been undertaken for early phase trials, a tabulated summary of the results of analytical method validation studies could be provided for further assurance.

Information for phase III clinical trials

Validation of the analytical methods used for release and stability testing should be provided. A tabulated summary of the results of the validation carried out should be submitted (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). By the end of phase III full method validation must be completed, including confirmation of robustness. It is not necessary to provide a full validation report.

S.4.4. Batch analyses

As the specification may initially be 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 clinical trial. For early phase clinical trials where only a limited number of batches of active substance have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For active substances with a 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 and any differences in these processes should be identified.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the IMPD might be used.

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 clinical development, the acceptance criteria may be wider and may not reflect process capability. 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 active substances, a well characterised reference material is essential to ensure consistency between different batches 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 adequately 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. Each in-house working standard should be qualified against this 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 standard should be established during development as primary reference material. The stability of the reference material should be monitored. This can be handled within the quality system of the company

S.6. Container closure system

The immediate packaging material used for the active substance should be stated. Possible interactions 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 the guidance given in 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 a container closure system of the same type and made from the same materials as that used to store active substance batches to be used in the clinical trial. 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 an extension of the shelf-life.

The methods used for analysing the stability-indicating properties of the active substance should be discussed, or cross-reference to S.4.3 made, 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.

A 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 made by a process representative of that used to manufacture material for use in the clinical trial. In addition, supportive stability data on relevant development batches or batches manufactured using previous manufacturing processes should be provided, if available. Such batch data may be used in the assignment of shelf life for the active substance provided an appropriate justification of the representative quality for the clinical trial material is given.

The relevant stability data 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. By 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 by relevant data, including accelerated stability studies and/or relevant stability data generated with representative material.

The maximum shelf-life after the extension should not be more than double, or more than twelve months longer than the period covered by real time stability data obtained with representative batch(es). However, extension of the shelf life beyond the intended duration of the long term stability studies is not acceptable.

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, and propose corrective actions.

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 active substance.

For shelf-life extension by way of substantial modification, see section 6.

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)
- an outline of the type of container and closure used for the dosage form and for any accompanying reconstitution diluent and devices, if applicable. A complete description should be provided in section P.7.

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 (e.g. reconstitution, dilution, mixing), 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) and 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 should 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. The batch sizes or range of batch sizes should be given.

P.3.3. Description of manufacturing process and process controls

A flow chart showing all steps of the manufacturing process, including relevant IPCs (process parameters and in-process-tests), should be provided accompanied by a brief process description. The IPCs may be recorded as action limits or reported as preliminary acceptance criteria and the focus should be on safety relevant attributes. For other IPCs, monitoring might be appropriate and acceptance criteria and action limits do not need to be reported. During development, as additional process knowledge is gained, further details of IPCs should be provided and acceptance criteria reviewed.

Most 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 Guideline on process validation for finished products - information and data to be provided in regulatory submissions, EMA/CHMP/CVMP/QWP/BWP/70278/2012).

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

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, duration 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. Test volumes of less than 100 ml may be used if justified.

P.3.5. Process validation

The state of validation of 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 of the same standard as for product authorised for marketing. The dossier should particularly include information directly relating to the product safety, i.e. on bioburden and media fill runs.

P.4. Control of excipients

P.4.1. Specification

References to Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP may be made. 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 note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01) 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/706271/2010). If the plasma derived component has already been used in a product with a Marketing Authorisation then reference to this can be made.

P.4.6. Novel excipients

For excipients 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 to 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 content, identity and purity are mandatory. Tests for sterility and endotoxins 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 impurities. They may need to be reviewed and adjusted during further development.

Acceptance criteria for IMP 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 into account safety considerations.

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. The 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 for all tests included in the specification should be described. 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 specifications may initially be 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 clinical trial. For early phase clinical trials where only a limited number of batches have been manufactured, test results from relevant clinical and non-clinical batches should be provided, including those to be used in the clinical trial supported by the IMPD. For products with a 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.

A statement should be included whether the batch analyses data presented are from the batches that will be used in the clinical trial, or whether additional batches not yet manufactured at time of submission of the IMPD might be used.

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 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 a medical device is to be used for administration it should be stated whether the device is CE marked for its intended purpose. In the absence of a CE mark for the intended purpose, a statement of compliance with the relevant essential requirements for medical devices with regards to safety and performance related device features is required. An integral device component of a drug-device combination product, as defined in the Medical Device Directive, is exempt from CE-marking.

For products intended for parenteral use where there is potential for interaction between product and container closure system, more details may be needed (e.g. extractable/leachable for phase III studies).

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.

In-use stability data should be presented for preparations intended for use after reconstitution, dilution, mixing or for multidose presentations. These studies are not required if the preparation is to be used immediately after opening or reconstitution.

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, an assessment of the risk with respect to potential viral contamination should be provided in this section. The documentation should comply with the requirements 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 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 should be provided.

3. Information on the quality of authorised, non-modified biological test and comparator products in clinical trials

Information on the authorised, non-modified test/comparator product provided in the IMPD should meet the requirements as outlined in section 3 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).

In the case when only repackaging is performed without changing the primary packaging, the following information should be included in the simplified IMPD in addition to the requirements listed in section 3 of EMA/CHMP/QWP/834816/2015:

- Information that will satisfy the requirement to ensure that the investigational medicinal product will have the proper identity, strength, quality and purity (e.g. cross-reference to the Summary of Product Characteristics for the EU marketed product).
- Details on the site of repackaging/relabeling operations.

4. Information on the quality of modified authorised biological comparator products in clinical trials

Information on the modified authorised test/comparator product provided in the IMPD should meet the requirements as outlined in this guideline.

Sections not impacted by the modification may cross-refer to the authorised product.

5. Information on the chemical and pharmaceutical quality concerning placebo products in clinical trials

Information on the placebo product to be provided in the IMPD should meet the requirements as outlined in section 6 of the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/834816/2015).

6. Changes to the investigational medicinal product and auxiliary medicinal product with a need to request a substantial modification to the IMPD

In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IMP/auxiliary medicinal product at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions. ~~The following is a non-exhaustive list of modifications that are typically 'substantial' and need to be notified to the competent authorities.~~

~~• changes in the 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 the 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~~

~~• changes to immediate packaging material, if the nature of material is changed~~

~~• changes in the approved in-use stability recommendations~~

~~• any extension of the shelf-life outside the agreed stability 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 modification if:~~

~~• each additional extension of the shelf-life is not more than double, and is not more than twelve months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol.~~

~~• 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~~

In compliance with the Clinical Trials Regulation (CTR), a change to IMP/auxiliary medicinal product quality data is either:

- a substantial modification (Art. 2.2.13);
- a change relevant to the supervision of the trial (Art. 81.9);
- a non-substantial modification (changes outside the scope of substantial modifications and changes irrelevant to the supervision of the trial).

Substantial modification means any change which is likely to have a substantial impact on the safety and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial. Assessment of an IMPD should be focussed on patient safety. Therefore, any modification involving a potential new risk has to be considered a substantial modification. This may be especially the case for changes in impurities profile, microbial contamination, viral safety, TSE and in some particular cases to stability when toxic degradation products may be generated.

Non-substantial modifications relevant to the supervision of the trial (Art 81.9 change) are concepts introduced under the CTR, which aims to update certain, specified information in the EU database (CTIS) without the need for a substantial modification application, when this information is necessary for oversight but does not have a substantial impact on patients safety and rights and/or data robustness. Art 81.9 states "The sponsor shall permanently update in the EU database information on any changes to the clinical trials which are not substantial modifications but are relevant for the supervision of the clinical trial by the Member States concerned". Art 81.9 changes can be submitted only if the change does not trigger additional changes, which are expected to be submitted as a substantial modification application. The combination of different Art 81.9 changes can cumulate into a change that needs to be submitted as a substantial modification.

For non-substantial modifications, documentation should not be proactively submitted, but the relevant internal and study documentation supporting the change should be recorded within the company and if appropriate, at investigator site. At the time of an overall IMPD update or submission of a substantial modification the non-substantial changes should be incorporated into the updated documentation. However, when submitting a modified IMPD, the sponsor should clearly identify which changes are substantial and which are not.

When a modification will become effective with the start of a new clinical trial (e.g. change of name of the IMP, new manufacturing process), the notification will take place with the application for the new trial. Submissions of substantial modifications are only necessary for changes in ongoing clinical trials.

In the following table, examples are given for changes in IMPs containing biological active substances, and their classification. This list does not claim to be exhaustive. The sponsor should decide on a case by case basis how to classify the change.

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
719	Change of name or code of the active substance or investigational medicinal product		• Change from company code to INN or trade name during ongoing clinical trial (exchange of the label)	
720	Manufacturer of the active substance	• Addition or replacement of manufacturing site or testing site • Change of manufacturer or change of manufacturing site (within the same company) • Deletion of manufacturing, or testing site (for safety reason, GMP non-compliance).		• Deletion of manufacturing, or testing site (no safety reason) • Name change of manufacturer

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
721	Manufacturing process of the active substance	Changes such as; • new expression cell line • new cell bank • change of a raw material of biological origin • changes to the viral safety tests performed on cell banks or unprocessed bulk batches, • change of production scale (upstream process), • changes to the cell culture conditions • changes in the purification process (downstream): addition or removal of a purification step • changes in the process		• Addition or tightening of IPC if not due to safety reasons • Modification of the process parameters (same process, analogous raw materials) where no effect on product quality is expected. • reprocessing if adequately described and accepted in the initial submission • minor changes in the manufacturing process which do not require a comparability exercise • changes to the controls of non critical raw materials

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
		conditions of a steps potentially effective on virus removal/inactivation, new virus validation studies (viral clearance studies) • any reprocessing not described in the IMPD • changes leading to the occurrence of new impurities and product related substances		
722	Specifications (release and shelf life) of the active substance	• change in the specification, if acceptance criteria are widened or test procedures are deleted or replaced • Replacement or deletion of a specification test based on supportive data		• Tightening acceptance criteria (no safety reason)

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
723	Analytical methods for control of the active substance	• New test methods and new test conditions		• Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided 1) the acceptance criteria are similar or tighter 2) the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results • Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results
724	Batch analysis of the active substance			• Additional batch data manufactured using the same process described in the IMPD unless it is

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
				requested otherwise
725	Reference standard			Introduction of new RS, provided equivalence has been established to the previous RS
726	Stability of the active substance	• changes in the approved storage conditions • any extension of the shelf-life outside the agreed stability protocol or without prior commitment • Reduction in shelf life due to stability concerns		• Additional intermediate stability timepoint but which is not yet covered (e.g., additional pull point at 42months) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension • Reduction in Shelf-Life if not safety or quality related Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if:

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
				• each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol • the extension is covered and in compliance with the approved stability protocol • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
727	Composition of the investigational medicinal product	• change to the formulation including changes in the active substance concentration and excipient • change of composition		
728	Manufacturer of the investigational medicinal product	• Addition or replacement of manufacturing site (including primary packaging) or testing site • Deletion of manufacturing, packaging or testing site (for safety reason, GMP non-compliance). • Addition or replacement of secondary packaging or labeling site with valid GMP status • Addition or		• Deletion of manufacturing, packaging or testing site (no safety reason) • Name change of manufacturer

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
		replacement of importation, QP release or QC testing sites		
729	Manufacturing process of the investigational medicinal product	• Significant changes to the manufacturing process		• Modifications of process parameters (same process) where no effect on product quality is demonstrated. • Scale-Up of filling process if supported by appropriate media fills.
730	Specifications (release and shelf life) of the investigational medicinal product	• change in the specification, if acceptance criteria are widened or test procedures are deleted or replaced • Replacement or deletion of specification test based on supportive data		• Tightening acceptance criteria (no safety reason)

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
731	Analytical methods for control of the investigational medicinal product	• New test methods and new test conditions		• Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided 1) the acceptance criteria are similar or tighter 2) the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results • Variation of the method already covered by the IMPD and the new test conditions are validated and lead to comparable or better validation results
732	Batch analysis of the investigational medicinal product			• Additional batch data manufactured using the same process described in the IMPD unless it is

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
				requested otherwise
733	Container closure system of the investigational medicinal product	• changes to immediate packaging		• Changes to secondary packaging • Change of supplier (deletion, replacement or addition) of packaging components if the material is identical and specifications are at least equivalent.
734	Medical devices registered in the IMPD	• Change to use a different medical device. • Changes to a medical device registered in the IMPD if potentially impacting on the quality, safety and/or efficacy.		• changes to a medical device registered in the IMPD which is not considered to impact on the quality, safety and/or efficacy.
735	Stability of the investigational medicinal	• changes in the		• Additional intermediate

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
	product	approved in-use stability recommendations • any extension of the shelf-life outside the agreed stability protocol or without prior commitment • Reduction in shelf life due to stability concerns		stability timepoint but which is not yet covered (e.g., add. pull point at 42m) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension • Reduction in Shelf-Life if not safety or quality related Shelf-life extension based on the agreed protocol is typically not considered as substantial modification if: • each additional extension of the shelf-life is not more than double and is not more than 12 months longer than available real time data and does not go beyond the duration as outlined in the agreed stability protocol

	Changes to IMPD	Substantial Modification (SM)	Art. 81.9 Non-substantial Modification (NSM)	Non-substantial Modification (NSM)
				• the extension is covered and in compliance with the approved stability protocol • no OOS results or significant trends which may lead to an OOS result during the approved shelf life have been detected in ongoing stability studies at the designated storage temperature