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

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This guideline replaces the “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials” (CHMP/QWP/185401/2004 final)

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1. Introduction

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 will often 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.

It should be clearly differentiated between the requirements for a dossier for a clinical trial and a marketing authorisation dossier. Whilst the latter ones have to ensure a state-of-the-art quality of a product for wide use in patients, information to be provided for investigational medicinal products (IMPs) should focus on the risk aspects and should consider the nature of the product, the state of development/clinical phase, patient population, nature and severity of the illness as well as type and duration of the clinical trial itself. As a consequence, it will not be possible to define very detailed requirements applicable to all sorts of different products. However, guidance on standard information which should normally be presented in the quality part of an IMPD is provided in this guideline.

1.2. Scope of the guideline

This guideline addresses the documentation on the chemical and pharmaceutical quality of IMPs and Auxiliary Medicinal Products containing chemically defined drug substances, synthetic peptides, synthetic oligonucleotides, herbal substances, herbal preparations and chemically defined radio-active/radio-labelled substances to be submitted to the competent authority for approval prior to beginning a clinical trial in humans. It includes the requirements for IMPs and Auxiliary Medicinal Products to be tested in phase I, phase II, phase III and phase IV studies as well as the requirements for modified and unmodified comparator products and IMPs to be tested in generic bioequivalence studies.

When compiling the quality part of the IMPD for phase II and phase III clinical studies, the larger and longer exposure of patients to the product have to be taken into account compared to phase I clinical studies. Based on the diversity of products to be used in the different phases of clinical trials, the requirements defined in this guideline can only be of an illustrative nature and cannot be expected to present an exhaustive list. IMPs based on innovative and/or complex technologies may need more detailed data to be submitted. For certain situations, e.g. where the drug substance from the specific source to be used for an IMP is already included in a medicinal product authorised within the EU, not all the documentation outlined in the following chapters need to be submitted in the IMPD, but a simplified IMPD will suffice.

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.

1.4. Submission of data

The IMPD should be provided in a clearly structured format following the numbering system as given in the chapters 2 to 8 of this Guideline. However, the first Arabic number being introduced only to facilitate the Guideline's use should be omitted.

The IMPD should include the most up-to-date information relevant to the clinical trial available at time of submission of the clinical trial application.

1.5. General considerations

For drug substances or IMPs to be used in clinical trials as described in chapters 2 to 8, reference to either the European Pharmacopoeia (Ph. Eur.), the Pharmacopoeia of an EU Member State, the United States Pharmacopoeia (USP) or the Japanese Pharmacopoeia (JP) is acceptable. For active substances, the suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) will have to be demonstrated by the applicant/sponsor. Suitability of monographs of the European Pharmacopoeia (Ph. Eur.) can be demonstrated with certificates of suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM). In other cases, information on the synthesis of the drug substance, including reagents, solvents, catalysts, and processing aids, should be provided.

For generic bioequivalence studies as described in chapter 5 which will support a Marketing Authorisation Application (MAA) in the EU, applicants/sponsors are advised that reference to the Ph. Eur. will facilitate future licensing activities in the EU.

For impurities in IMPs, a justification that the product is safe for its intended use, considering the anticipated exposure of volunteers and patients, respectively, will be required.

When compiling the documentation, the difference between "analytical procedure" and "analytical method" should be kept in mind. The term "analytical procedure" is defined in ICH Q 2 (A) and refers to the way of performing the analysis. The term "analytical method" refers to the principles of the method used.

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

2.2.1.S Drug substance

Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicines is acceptable. The procedure as described in the "Guideline on Active Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr" and the "Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1" in their current version should be followed, even though no specific reference to clinical trials application is included.

For reference to pharmacopoeial monographs, see chapter 1.5 General Considerations.

If the Active substance used is already authorised in a drug product within the EU/EEA or in one of the ICH-regions, reference can be made to the valid marketing authorisation. A statement from Marketing Authorisation Holder or drug substance manufacturer should be provided that the active substance has the same quality as in the approved product.

Name of the drug product, marketing authorisation number or its equivalent, marketing authorisation holder and the country that granted the marketing authorisation should be given.

2.2.1.S.1 General information

2.2.1.S.1.1 Nomenclature

Information concerning the nomenclature of the drug substance (e.g. INN-name (if approved), pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other names or codes, if any) should be given. In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans to develop a non-radioactive medicinal product, the radio-nuclide or the radio-labelled substance should be stated additionally.

For radio-nuclides, the isotope type should be stated (IUPAC-nomenclature).

In the case of radio-nuclide generators, both parent radio-nuclide and daughter radio-nuclide are considered as drug substances. For kits, which are to be radio-labelled, the part of the formulation which will carry or bind the radio-nuclide should be stated as well as the radio-labelled product. For organic-chemical precursors, the same information should be provided as for drug substances.

For herbal substances the binominal scientific name of the plant (genus, species, variety and author) and the chemotype as well as the parts of the plant, the definition of the herbal substance, other names (synonyms mentioned in other Pharmacopoeias) and the laboratory code should be provided.

In addition, for herbal preparations the ratio of the herbal substance to the herbal preparation as well as the extraction solvent(s) used for extraction should be stated.

2.2.1.S.1.2 Structure

The data available at the respective stage of clinical development should be presented. They should include the structural formula, molecular weight, and chirality/stereochemistry as far as elucidated.

In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans to develop a non-radioactive medicinal product, the structural formula before and – if known – after the radio-labelling should be given. For kits for radiopharmaceutical preparations, the ligand's structural formula before and, if known, after the radio-labelling should be given.

In addition, the physical state, the extract type, if known the constituent(s) relevant for the therapeutic activity or the analytical marker substance(s) used should be stated for herbal substances and herbal preparations. Information about excipients in the final herbal preparations should be provided.

2.2.1.S.1.3 General properties

A list of physico-chemical and other relevant properties of the active substance should be provided, in particular physico-chemical properties that could affect pharmacological or toxicological safety, such as solubilities, pKa, polymorphism, isomerism, log P, permeability etc..

For radio-nuclides, the nuclear and radiophysical properties should be stated. Their source should be also specified, i.e. whether fission or non-fission.

2.2.1.S.2 Manufacture

2.2.1.S.2.1 Manufacturer(s)

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

In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans to develop a non-radioactive medicinal product, the manufacturer should be stated. For radiopharmaceuticals, the manufacturer of the radiopharmaceutical precursors and of non-radioactive precursors should be stated, as well as the source of any cyclotron irradiation target materials and production site(s) at which irradiation occurs.

2.2.1.S.2.2 Description of manufacturing process and process controls

For chemical substances: A brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and critical reagents used should be provided. Drug substance manufacturing process should be described in the IMPD in such extent so it is understood how impurities are introduced in the process, and why the proposed control strategy is suitable. This will typically include a description of multiple chemical transformation steps. Any relevant process controls should be indicated. Where critical steps in the synthesis have been identified, a more detailed description may be appropriate. The stereo-chemical properties of starting materials should be discussed, where applicable. For substances which comply to 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 monographs is acceptable, but suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) should be discussed by submission of sufficient information on the manufacturing process of the active substance (see chapter 1.5 General Considerations).

For radio-nuclides, the manufacturing process, as well as nuclear reactions should be described, including possible undesired nuclear reactions. The conditions for irradiation should be given. The cleaning and segregation processes for the radiopharmaceutical preparation and the organo-chemical precursors should be stated.

For herbal substances or herbal preparations, a brief summary of the manufacturing process and a flow chart of the successive steps, starting with the plant cultivation or the plant collection, should be provided. The in-process controls carried out should be documented. The main production steps should be indicated.

2.2.1.S.2.3 Control of materials

Materials used in the manufacture of the drug substance (e.g. raw materials, starting materials, solvents, reagents, catalysts) should be listed together with a brief summary on the quality and control of any attributes anticipated to be critical, for example, where control is required to limit an impurity in the drug substance, e.g. chiral control, metal catalyst control or control of a precursor to a potential genotoxic impurity. For radio-nuclides, details on the target material should be given.

2.2.1.S.2.4 Control of critical steps and intermediates

In case of critical steps in the synthesis, tests and acceptance criteria for their control should be briefly summarised.

2.2.1.S.2.5 Process validation and/or evaluation

Not applicable for drug substances to be used in clinical trials.

2.2.1.S.2.6. Manufacturing process development

It should be documented if the manufacturing process significantly differs from that used for the production of the batches used in the non-clinical studies. In this case, a flow chart of the manufacturing process used for the drug substance used in the non-clinical studies should be presented.

Significant changes in the manufacturing process, which may impact on quality, should be discussed (e.g. change of route of synthesis).

2.2.1.S.3 Characterisation

2.2.1.S.3.1 Elucidation of structure and other characteristics

The structure of chemically defined substances should be established with suitable methodology; relevant data should be provided.

For radiopharmaceutical substances, the analogous non-radioactive substances should be used to determine the structure. For radiopharmaceutical kits the structure of the radiolabelled compound should be described where possible.

For herbal substances, information should be given on the botanical, macroscopic and microscopic and phytochemical characterisation. Where applicable, details should be given on the biological activity. For herbal preparations, details should be provided on the physical and phytochemical characterisation. Where applicable, details should be given on the biological activity.

2.2.1.S.3.2 Impurities

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been discussed.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities (e.g. degradation products, residual solvents) deriving from the manufacturing process or starting materials relevant to the drug substance used for the clinical trial, should be stated.

Discussion on (potential) mutagenic impurities according to ICH M7 should be provided (structure, origin, limit justification). The level of detail necessary depends on the phase of the clinical trial.

Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans to develop a non-radioactive medicinal product, the radiochemical purity and the chemical purity should be indicated describing any assumptions made, e.g. as a consequence of the determination

being made prior to dilution with cold material. For radiopharmaceutical substances, the radio-nuclidic purity, the radiochemical purity and the chemical purity should be stated and discussed.

For herbal substances or herbal preparations, data on potential contamination by micro-organisms, products of micro-organisms, aflatoxins, pesticides, toxic metals, radioactive contamination, fumigants, etc. should be stated. The general requirements of the Ph. Eur. should be fulfilled.

2.2.1.S.4 Control of the Drug Substance

2.2.1.S.4.1 Specification(s)

The specifications, the tests used as well as their acceptance criteria should be specified for the batch(es) of drug substance(s) used in the clinical trial. Tests for identity, impurities and assay are mandatory. Upper limits, taking safety considerations into account, should be set for the impurities. They may need to be reviewed and adjusted during further development. The limits should be supported by the impurity profiles of batches of active substance used in non-clinical and clinical studies. If ICH or Ph.Eur. requirements are met, no further limit justification is expected.

Where specifications are set for (potential) mutagenic impurities, the guidance given in relevant guidelines should be taken into consideration.

The microbiological quality for drug substances used in aseptically manufactured products should be specified.

For substances 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 sufficient, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvent or catalyst.

For radiopharmaceutical drug substances, the level of radio-nuclidic impurities, radiochemical impurities as well as the chemical impurities should be addressed.

Additional information for phase II and phase III clinical trials

Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.

2.2.1.S.4.2 Analytical procedures

The analytical methods used for the drug substance should be described for all tests included in the specification (e.g. reverse-phase-HPLC-UV, potentiometric titration, head-space-GC-FID, etc.). It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General Considerations).

For radiopharmaceutical substances, the method used for the measurement of radioactivity should be described.

For substances 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 sufficient.

2.2.1.S.4.3 Validation of analytical procedures

Information 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.

For substances 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 sufficient.

In case of major changes in analytical methods, cross-validation data should be presented especially for specified unknown impurities identified by their relative retention time (RRT) unless otherwise justified. A re-analysis of preclinical batch with the new method should also be considered, where relevant.

2.2.1.S.4.4 Batch analyses

Batch results in a tabulated form or certificate of analysis for batches to be used in the current clinical trial, for batches used in the non-clinical studies and, where needed, for representative batches used in previous clinical trials (e.g. in case the comparable quality of batches manufactured by previous processes has to be demonstrated), should be supplied. If data are not available for the batches to be used in the current clinical trial, data for representative batches for each drug substance manufacturer may be submitted instead. The batch number, batch size, manufacturing site, manufacturing date, control methods, and the test results should be listed.

The manufacturing process used for each batch should be assigned as stated under 2.2.1.S.2.2.

2.2.1.S.4.5 Justification of specification(s)

For substances for which reference to a pharmacopoeial monograph listed under 2.2.1.S.4.1 cannot be made, a brief justification of the specifications and acceptance criteria for impurities and any other parameters which may be relevant to the performance of the drug product should be provided based on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and catalysts used in the synthesis should be taken into consideration.

2.2.1.S.5 Reference standards or materials

The parameters characterising the batch of drug substance established as reference standard should be presented, where applicable.

For radiopharmaceuticals, data on the standards used for calibration and the non-radioactive (cold) standards should be provided.

For herbal preparations, the parameters characterising the primary reference standards should be given. In cases where the herbal substance is not described in a monograph of the Ph. Eur. or a monograph in the pharmacopoeia of an EU Member State, a characterised herbarium sample should be available.

2.2.1.S.6 Container closure system

The immediate packaging material used for the drug substance should be stated. If non-compendial materials are used, a description and specifications should be provided.

2.2.1.S.7 Stability

The stability data available at the respective stage of development should be summarised in tables. Stability data should be provided for batch(es) manufactured according to the representative process (the same/very similar synthesis, comparable batch size) and can be supported by data from batch(es) manufactured by previous processes. The parameters known to be critical for the stability of the drug substance need to be presented, i.e. chemical and physical sensitivity, e.g. photosensitivity, hygroscopicity. Potential degradation pathways should be described. Alternatively, for active substances covered by a pharmacopoeial monograph, confirmation that the active substance will meet specifications at time of use will be acceptable.

The retest period should be defined based on the available stability data and should be clearly stated. For drug substances covered by a Certificate of Suitability (CEP) which does not include a retest date, supporting stability data and a retest period should be provided. In case no retest period is defined, statement should be included that the drug substance is tested immediately before the drug product manufacture.

The retest period can be extended without a substantial modification submission, if a stability protocol, retest period extension plan and a statement that in case of any significant negative trend the Sponsor will inform the competent authority are provided. The stability protocol should cover the maximum planned re-test period.

For herbal preparations, results of stress testing may be omitted, where justified.

2.2.1.P Investigational medicinal product under test

2.2.1.P.1 Description and composition of the investigational medicinal product

The complete qualitative and quantitative composition of the IMP should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form and the function of each excipient should be included. Standard terminology from the EDQM standard terms database should be preferably used for dosage forms, where applicable.

In addition, the radioactivity per unit should be specified for radiopharmaceuticals. Radioactivity should only be expressed in Becquerel at a given date, and time if appropriate. If a calibration time is stated, the time zone used should be stated (e.g. GMT/CET).

2.2.1.P.2 Pharmaceutical development

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

For early development, there may be no or only limited information to include in this section.

The medicinal product components, the dosage form and the administration device if any should be safe and suitable for the patient population.

Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures should be demonstrated. For products to be reconstituted or diluted prior to their use, the method of preparation should be summarised and reference made to a full description in the clinical protocol or associated handling instructions which will be available at the clinical site should be provided.

For kits for radiopharmaceutical preparations, the suitability of the method used for the radio-labelling for the intended use should be demonstrated (including results on the physiological distribution after radio-labelling in rats/rodents). For radio-nuclide generators, the suitability of the elution medium should be proven. For radiopharmaceuticals, the effect of radiolysis on the purity should be addressed.

Additional information for phase II and phase III clinical trials

If changes in the formulation or dosage form compared to the IMP used in earlier clinical trials have been made, the relevance of the earlier material compared to the product under testing should be described. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

2.2.1.P.2.1 Manufacturing process development

Changes in the current manufacturing process compared to the ones used in earlier clinical trials are to be explained. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

2.2.1.P.3 Manufacture

2.2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in manufacture, packaging/assembly and testing should be provided. In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated. Site(s) responsible for import or/and QP release in the EEA should be also stated.

When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the Regulation (EU) No. 536/2014 applies, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

2.2.1.P.3.2 Batch formula

The batch formula for the batch to be used for the clinical trial should be presented. Where relevant, an appropriate range of batch sizes may be given.

2.2.1.P.3.3 Description of manufacturing process and process controls

A flow chart of the successive steps, indicating the components used for each step and including any relevant in-process controls, should be provided. In addition, a brief narrative description of the manufacturing process should be included.

Non-standard manufacturing processes or new technologies and new packaging processes should be described in more detail (c.f. Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03)).

2.2.1.P.3.4 Controls of critical steps and intermediates

Information is not required for phase I and II clinical trials, with the exception of:

- Non-standard manufacturing processes; and
- Manufacturing processes for sterile products.

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, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If availability of the formulated medicinal product is limited, a prefiltration/filtration volume of less than 100 ml may be tested if justified.

Statement that aseptic processing operations were validated using media fill runs should be provided.

Additional information for phase III clinical trials

If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.

Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

2.2.1.P.3.5 Process validation and/or evaluation

Data are not required during the development phases, i.e. clinical phases I to III, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

2.2.1.P.4 Control of excipients

2.2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film- coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

2.2.1.P.4.2 Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under 2.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

2.2.1.P.4.3 Validation of the analytical procedures

Not applicable.

2.2.1.P.4.4 Justification of specifications

Not applicable.

2.2.1.P.4.5 Excipients of animal or human origin

Cf. section 7.2.1.A.2.

2.2.1.P.4.6 Novel excipients

For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be provided in annex 2.1.A.3 consistent with the respective clinical phase (c.f. section 7.2.1.A.3), details are to be included on e.g. their manufacturing process, characterisation and stability.

2.2.1.P.5 Control of the investigational medicinal product

2.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. At least, tests on identity, assay and degradation products should be included for any pharmaceutical form.

Upper limits may be set for both individual degradation products and the sum of degradation products. Safety considerations should be taken into account. The limits should be supported by the impurity profiles of batches of active substance used in non-clinical/clinical studies. The specifications and acceptance criteria should be reviewed and adjusted during further development.

Drug product specific tests and acceptance criteria should be included in the specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral dosage forms).

The omission of drug product specific tests should be justified.

For radiopharmaceuticals, it should be specified which tests are carried out prior to batch release and which tests are carried out retrospectively. For kits for radiopharmaceutical preparations, appropriate tests after radioactive radio-labelling should be stated.

For medicinal products to be reconstituted or diluted prior to their use, the acceptable quality standard after preparation should be stated and documented by development testing.

Additional information for phase II and phase III clinical trials

Specifications and acceptance criteria set for previous phase I or phase II trials should be reviewed and, where appropriate, adjusted to the current stage of development.

2.2.1.P.5.2 Analytical procedures

The analytical methods should be described for all tests included in the specification (e.g. dissolution test method). It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

For complex or innovative pharmaceutical forms, a higher level of detail may be required.

2.2.1.P.5.3 Validation of analytical procedures

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.

Additional 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 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.

2.2.1.P.5.4 Batch analyses

Batch results in a tabulated form or certificates of analysis for representative batches (same manufacturing site, same manufacturing process, same composition, and comparable batch size, unless otherwise justified,) to be used in the clinical trial should be provided. The results should cover the relevant strengths to be used in the trial.

The batch number, batch size, manufacturing site, manufacturing date, control methods, and the test results should be listed.

In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which have been produced by each of the bulk manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch analysis data from one site only would be sufficient).

Results for batches controlled according to previous, wider specifications are acceptable if the results comply with the specifications for the planned clinical trial.

2.2.1.P.5.5 Characterisation of impurities

Additional impurities/degradants observed in the IMP, but not covered by section 2.2.1.S.3.2, should be stated.

2.2.1.P.5.6 Justification of specification(s)

For IMPs in phase I clinical trials, it will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. Toxicological justification should be given, where appropriate.

Additional information for phase II and phase III clinical trials

The choice of specifications and acceptance criteria for parameters which may affect efficacy or safety should be briefly justified.

2.2.1.P.6 Reference standards or materials

The parameters for characterisation of the reference standard should be submitted, where applicable. Section 2.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable. For radiopharmaceuticals, information should be provided on radioactive standards used in the calibration of radioactivity measurement equipment.

2.2.1.P.7 Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions), more details may be needed for phase III studies (e.g. extractables, leachables). For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

2.2.1.P.8 Stability

The shelf-life and storage conditions of the IMP should be defined based on the stability profile of the active substance and the available data on the IMP. Stability data for representative batch(es) should be provided in a tabulated form. Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical studies and throughout its entire duration. Shelf life extrapolation can be made under the following conditions:

- Results at long-term as well as at accelerated storage conditions are available;
- No significant changes in stability behaviour are observed. If any observed, justification should be provided;

- Stability protocol covering the proposed extrapolated shelf life should be provided;
- Criteria used to extrapolate data should be clearly defined; and
- Depending on the data available:
    - A fourfold extrapolation of accelerated stability data may be acceptable up to a shelf life of 12 months
    - An extrapolation of + max 12 months to long-term stability data available (at least 6-months) may be acceptable for a shelf life of more than 12 months
    - Other schemes may be possible but should be justified.

Furthermore, bracketing and matrixing designs of appropriate IMPs may be acceptable, where justified. The batches of drug product must meet specification requirements throughout the period of use. If issues arise, then the Competent Authorities should be informed of the situation, including any corrective action proposed.

In case the drug product is stored in a bulk for a significant time period, relevant stability data should be provided as well as shelf life, storage conditions and packaging material for the bulk. In case the final drug product shelf life is calculated not from the first mixing of the drug substance with excipients but from the time of packaging into the primary package, this should be clearly stated and justified.

Any proposal for a future shelf life extension without substantial modification submission should be stated in the IMPD. Stability protocol, shelf life extension plan and a statement that in case of any significant negative trend the Sponsor will inform the competent authority should be provided. The stability protocol should cover the maximum planned shelf life.

For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In-use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and sub-visible particles, microbial contamination). Shelf life and storage conditions after first opening and/or after reconstitution and/or dilution should be defined. These studies are not required if the preparation is to be used immediately after opening or reconstitution and if it can be justified that no negative influence on the quality of the preparation through instabilities is to be expected.

For radiopharmaceuticals, the time of calibration should be specified, since the stability also depends on the half-life of the radioactive isotope.

Information for phase I clinical trials

For phase I clinical trials, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. Where available, the results from these studies should be summarised in a tabulated form. Supportive data from development studies should be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IMP in the clinical trial should be provided.

Additional information for phase II and phase III clinical trials

The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf- life to be assigned to the IMP in the clinical trial should be provided. Data should include results from studies under accelerated and long-term storage conditions.

For radiopharmaceuticals, the time of calibration should be specified. The general stability guidelines are not fully applicable for ready-for-use radiopharmaceuticals, radio-nuclide generators and radioactive precursors. However, the aspects reflected in the Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) should be taken into consideration.

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

For test and comparator products to be used in clinical trials which have already been authorised in the EU/EEA or in one of the ICH-regions (and are sourced from these countries), it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA, incl. copy of the SmPC/Summary of Product Characteristics or its equivalent e.g. Prescribing information. For repackaged/modified authorised products, see following chapter.

The applicant or sponsor of the clinical trial has to ensure that the IMP is stable at least for the anticipated duration of the clinical trial in which it will be used. For authorised, not modified products, it will be sufficient to state that the respective expiry date assigned by the manufacturer will be used.

For IMPs sourced from outside of the EU/EEA or ICH regions, a full documentation, according to the requirements stated in chapter 2 of this guideline, should be submitted.

4. Information on the chemical and pharmaceutical quality of modified authorised test and comparator products in clinical trials

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

As the marketing authorisation holder (MAH) of an authorised product is only responsible for the un-changed product in its designated and authorised packaging, there is a need to ensure that the quality of the product is not negatively affected by the modifications performed by the applicant or sponsor of the clinical trial, with special emphasis on the biopharmaceutical properties.

4.2.1.P Modified test/comparator product

4.2.1.P.1 Description and composition

In the case of any modification of the authorised product other than repackaging, the complete quantitative composition of the preparation should be specified. All additional substances/materials added to the authorised product should be listed with reference to pharmacopoeial or in-house monographs. For the authorised product itself, reference to the name and marketing authorisation (MA) number will suffice, including a copy of the SPC/PIL in Module 1.

4.2.1.P.2 Pharmaceutical development

The modifications carried out on the authorised product should be described and their influence on the quality of the product discussed. Special focus should be assigned to all parameters relevant for the function, stability and efficacy of the medicinal product, such as in vitro-dissolution and pH-value. It should be demonstrated that these parameters remain comparable to those of the unmodified product.

Compatibility with other solvents (that are not stated in the original SmPC) used for drug product reconstitution and dilution should be demonstrated. Compatibility studies reflecting the practice described in the clinical protocol (e.g. dispersion of a tablet or content of the hard capsule in water/juice/food) should be performed in case of unstable products and/or in case of preparation in advance.

In case of solid oral dosage forms, comparative dissolution profiles of both original and modified product should be provided to ensure unchanged bio-pharmaceutical properties. In those cases where comparability cannot be established in vitro, additional clinical data to support equivalence may be necessary.

4.2.1.P.3 Manufacture

4.2.1.P.3.1 Manufacturer(s) related to the modification

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in the modification, packaging/assembly and testing of the modified product should be provided. In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated. Sites responsible for import or/and QP release in the EEA should be also stated.

When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the Regulation (EU) No. 536/2014 applies, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

4.2.1.P.3.2 Batch formula

The batch formula for the batch intended to be used during the clinical trial should be presented. This does not apply to authorised products which are only re-packaged.

4.2.1.P.3.3 Description of manufacturing process and process controls

All steps of the modification of the authorised medicinal product should be described, including in-process controls that are carried out. For details, reference is made to section. 2.2.1.P.3.3).

4.2.1.P.4 Control of excipients

4.2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-

chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

4.2.1.P.4.2 Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under 4.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

4.2.1.P.4.3 Validation of analytical procedures

Not applicable.

4.2.1.P.4.4 Justification of specifications

Not applicable.

4.2.1.P.4.5 Excipients of animal or human origin

Cf. Appendix 7.2.1.A.2.

4.2.1.P.5 Control of the modified authorised product

4.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications of the modified authorised product should be submitted, including test methods and acceptance criteria. Generally, they should include description and identification of the drug substance as well as the control of important pharmaceutical and technological properties, such as dissolution. Where an intact solid oral dosage form that is easily identifiable by its colour, shape and marking is encapsulated, identification of the active substance may not be necessary, and visual examination may suffice for identification. Depending on the degree of modification of the authorised product, additional quality criteria, e.g. determination of the drug substance(s) and impurities/degradants, may need to be specified and tested.

4.2.1.P.5.2 Analytical procedures

For parameters relevant to the performance of the modified authorised product, e.g. dissolution, the methods should be described. It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

4.2.1.P.5.3 Validation of analytical procedures

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods 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.

4.2.1.P.5.4 Batch analyses

Results or certificates of analysis for the batch of modified authorised product to be used in the clinical trial or of a representative batch should be provided.

In case of more than one bulk manufacturing sites, it is necessary to provide results for batches which have been produced by each of the bulk manufacturing sites relevant for the current trial unless otherwise justified, (e.g. where one legal entity has multiple sites (in the same country), then batch analysis data from one site only would be sufficient).

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

4.2.1.P.5.5 Characterisation of impurities

In those cases, where the authorised product has undergone significant modification by the sponsor, e.g. has been processed with an excipient hitherto not present in the formulation with a likely impact on product stability, and the original product is not known to be stable under normal conditions, special emphasis should be given to demonstrating that the impurity profile has not changed compared to the original product. For stable authorised products, where a small degree of modification has been undertaken by the sponsor, e.g. where an intact tablet is encapsulated using the ingredients already present in the tablet, justification for not quantifying impurities will suffice (for definition of “stable” cf. Note for Guidance on Stability Testing of New Drug Substances and Products (CPMP/QWP/2736/99), section 2.2.7 “Storage conditions”). This is not required for authorised products which are only re-packaged.

4.2.1.P.5.6 Justification of specification(s)

A justification of specification(s) will only be required in cases where a significant modification of the authorised product may affect the product’s performance or safety.

4.2.1.P.7 Container closure system

The type of immediate packaging, material and package size(s) should be specified. If materials other than those authorised are used, a description and specifications should be provided. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the test/comparator product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided.

4.2.1.P.8 Stability

The applicant or sponsor of the clinical trial has to ensure that the modified test/comparator product is stable for at least the anticipated duration of the clinical trial in which it will be used.

In the case of any modification with a likely significant impact on product stability, a minimum of stability data on the modified authorised product should be available, depending on the length of the planned clinical trial, prior to the start of the clinical trial in order to allow an assessment of the impact of the modifications on product safety and stability. The available stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be

assigned to the IMP in the clinical trial should be provided. Any degree of extrapolation may not exceed the shelf-life originally assigned to the specific batch of authorised product by its MAH.

Shelf life extension without a substantial modification submission can be approved under the same conditions as described in the section 2.2.1.P.8.

In the case of only minor modifications, a justification of the stability over the intended trial period may be acceptable.

In-use stability studies should be performed in case of use of the comparator product in different conditions as those described in the SPC (according to the clinical protocol), if not otherwise justified (the same requirements as defined in section 2.2.1.P.8 apply).

5. Information on the chemical and pharmaceutical quality of investigational medicinal products containing existing active substances used in bio-equivalence studies, e.g. generics (chemical substances)

This section of the guideline is only relevant for the test product. Information on the comparator/innovator product to be provided in the IMPD should meet the requirements as outlined in sections 3 and 4, respectively.

5.2.1.S Drug substance

Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicines is acceptable. The procedure as described in the “Guideline on Active Substance Master File Procedure – CPMP/QWP/227/02 Rev 3 corr” and the “Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier – CHMP/QWP/297/97 Rev 1” in their current version should be followed, even though no specific reference to clinical trials application is included.

For reference to pharmacopoeial monographs, see chapter 1.5 General Considerations.

If the Active substance used is already authorised in a drug product within the EU/EEA or in one of the ICH-regions, reference can be made to the valid marketing authorisation. A statement should be provided that the active substance has the same quality as in the approved product.

Name of the drug product, marketing authorisation number or its equivalent, marketing authorisation holder and the country that granted the marketing authorisation should be given.

5.2.1.S.1 General information

5.2.1.S.1.1 Nomenclature

Information concerning the nomenclature of the drug substance (e.g. (proposed) INN-name, pharmacopoeial name, chemical name, code, and other names, if any) should be given.

5.2.1.S.1.2 Structure

The structural formula should be presented.

5.2.1.S.1.3 General Properties

The main physicochemical and other relevant properties of the drug substance should be indicated.

5.2.1.S.2 Manufacture

5.2.1.S.2.1 Manufacturer(s)

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

5.2.1.S.2.2 Description of manufacturing process and process controls

For substances which comply to 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 monographs is acceptable, but suitability of the referenced monograph to adequately control the quality of the active substance (impurity profile) should be discussed by submission of sufficient information on the manufacturing process of the active substance (see section 1.5).

In cases where reference to a pharmacopoeial monograph listed above cannot be made, a brief summary of the synthesis process, a flow chart of the successive steps including, for each step, the starting materials, intermediates, solvents, catalysts and reagents used should be provided. The stereo-chemical properties of starting materials should be discussed, where applicable.

5.2.1.S.3 Characterisation

5.2.1.S.3.2 Impurities

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been discussed.

Discussion on (potential) mutagenic impurities should be provided (structure, origin, limit justification), if relevant.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, impurities (e.g. possible degradation products and residual solvents), deriving from the manufacturing process or starting materials relevant to the drug substance used for the bio-equivalence study should be stated.

Absence of routine control for solvents/catalysts used in the manufacturing process should be justified.

5.2.1.S.4 Control of the drug substance

5.2.1.S.4.1 Specifications

The microbiological quality of drug substances used in aseptically manufactured products should be specified.

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications, tests used as well as the acceptance criteria should be provided for the batch(es) of the drug substance(s) intended for use in the bio-equivalence study. Tests for identity and assay are mandatory. Upper limits, taking safety considerations into account, should be set for the impurities. Where specifications are set for (potential) mutagenic impurities, the guidance given in relevant guidelines should be taken into consideration.

5.2.1.S.4.2 Analytical procedures

For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 of this chapter cannot be made, the analytical methods used for the drug substance (e.g. reverse- phase-HPLC-UV, potentiometric titration, head-space-GC-FID, etc.) should be provided. It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General Considerations).

5.2.1.S.4.3 Validation of analytical procedures

For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 of this chapter cannot be made, the suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. values found for repeatability, limit of quantification etc.). It is not necessary to provide a full validation report.

5.2.1.S.4.4 Batch analyses

Certificates of analyses or batch analysis data for the batch(es) intended for use in the planned bio-equivalence study or, in their absence, for representative batches, should be supplied. The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and test results should be listed.

5.2.1.S.4.5 Justification of specifications

For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 cannot be made, a brief justification of the specifications and acceptance criteria for impurities and any other parameters which may be relevant to the performance of the drug product should be provided based on safety and toxicity data, as well as the methods used for the control of impurities. The solvents and catalysts used in the synthesis should be taken into consideration.

5.2.1.S.5 Reference Standards or materials

For substances for which reference to a pharmacopoeial monograph listed under 5.2.1.S.4.1 cannot be made, the parameters characterising the batch of drug substance established as reference standards should be presented.

5.2.1.S.6 Container closure system

The immediate packaging material used for the drug substance should be stated. If non-compendial materials are used, a description and specifications should be provided.

5.2.1.S.7 Stability

The available stability data should be provided in a tabulated form. The retest period should be defined based on the available stability data and should be clearly stated. For drug substances covered by a Certificate of Suitability (CEP) which does not include a retest date, supporting stability data and a retest period should be provided. In case no retest period is defined, statement should be included that the drug substance is tested immediately before the drug product manufacture.

5.2.1.P Investigational medicinal product under test

5.2.1.P.1 Description and composition

The complete qualitative and quantitative composition of the IMP should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. Standard terminology from the EDQM standard terms database should be preferably used for dosage forms, where applicable.

5.2.1.P.2 Pharmaceutical development

A brief narrative description of the dosage form should be provided.

5.2.1.P.3 Manufacture

5.2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in manufacture, packaging/assembly and testing should be provided. In case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities in the manufacturing chain should be clearly indicated. Site(s) responsible for import or/and QP release in the EEA should be also stated.

When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the Regulation (EU) No. 536/2014, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

5.2.1.P.3.2 Batch formula

The batch formula for the batch to be used in the planned bio-equivalence study should be presented. Where relevant, an appropriate range of batch sizes may be given.

5.2.1.P.3.3 Description of manufacturing process and process controls

A flow chart of the successive steps, including the components used for each step and including any relevant in process controls, should be provided. In addition, a brief narrative description of the manufacturing process should be included.

5.2.1.P.3.4 Control of critical steps and intermediates

If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.

Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

5.2.1.P.3.5 Process validation and/or evaluation

Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

5.2.1.P.4 Control of excipients

5.2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

5.2.1.P.4.2 Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under 5.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

5.2.1.P.4.3 Validation of analytical procedures

Not applicable.

5.2.1.P.4.4 Justification of specifications

Not applicable.

5.2.1.P.4.5 Excipients of animal or human origin

Cf. Appendix 7.2.1.A.2.

5.2.1.P.4.6 Novel excipients

For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be provided in annex 2.1.A.3 consistent with the respective clinical phase (c.f. section 7.2.1.A.3), details are to be included on e.g. their manufacturing process, characterisation and stability.

5.2.1.P.5 Control of the investigational medicinal product

5.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. At least, tests on identity, assay and degradation products should be included for any pharmaceutical form. Drug product specific tests defined in the Ph.Eur. monographs for dosage forms (see chapter 1.5 General Considerations) and acceptance criteria should be included in the specifications in line with the pharmaceutical form used (e.g. dissolution/disintegration for oral solid dosage forms; uniformity of dosage units; or pH, bacterial endotoxins and sterility for parenteral dosage forms).

The omission of drug product specific tests should be justified.

5.2.1.P.5.2 Analytical procedures

The analytical methods should be described for all tests included in the specification (e.g. dissolution test method). It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

For complex or innovative pharmaceutical forms, a higher level of detail may be required.

5.2.1.P.5.3 Validation of analytical procedures

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the validation results 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.

5.2.1.P.5.4 Batch analyses

Certificates of analysis or batch analysis data for the batch(es) intended to be used in the planned bio-equivalence study or, in their absence, representative batches, should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

5.2.1.P.5.5 Characterisation of impurities

Additional impurities/degradants observed in the IMP, but not covered by section 5.2.1.S.3.2, should be stated.

5.2.1.P.5.6 Justification of specification(s)

It will be sufficient to briefly justify the specifications and acceptance criteria for degradation products and any other parameters that may be relevant to the performance of the drug product. Toxicological justification should be given, where appropriate.

5.2.1.P.6 Reference standards or materials

The parameters for characterisation of the reference standard should be submitted, if no compendial reference standard is available.

Section 5.2.1.S.5 – Reference Standards or Materials – may be referred to, where applicable.

5.2.1.P.7 Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IMP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided. For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic products, oral solutions), more details may be needed. For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

5.2.1.P.8 Stability

For bioequivalence studies, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. The results from at least one month accelerated studies or the results of the initial phase of studies under long-term storage conditions should be summarised in a tabulated form. Supporting data from development studies should also be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life and storage conditions to be assigned to the IMP in the bio-equivalence study should be provided. Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study.

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

The quality documentation to be submitted for placebos is limited to the following sections of the product part.

6.2.1.P Placebo product in clinical trials

6.2.1.P.1 Description and composition

The complete qualitative and quantitative composition of the placebo should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient. A short statement or a tabulation of the dosage form and the function of each excipient should be included.

6.2.1.P.2 Pharmaceutical development

It should be described how possible differences of the placebo preparation in relation to the investigational medicinal product regarding taste, appearance and smell are masked, where applicable.

6.2.1.P.3 Manufacture

6.2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed site involved in manufacture, packaging/assembly and testing should be provided. In case that multiple manufacturers contribute to the manufacture of the placebo, their respective responsibilities need to be clearly stated.

When re-packaging and or re-labelling is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, as provided for in article 61 (5) of the Regulation (EU) No. 536/2014, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

6.2.1.P.3.2 Batch formula

The batch formula for the batch to be used for the clinical trial should be presented. Where relevant, an appropriate range of batch sizes may be given.

6.2.1.P.3.3 Description of manufacturing process and process controls

A flow chart of the successive steps, indicating the components used for each step and including in-process controls should be provided. In addition, a brief narrative description of the manufacturing process should be included.

6.2.1.P.3.4 Control of critical steps and intermediates

Information is not required with the exception of manufacturing processes for sterile products (the same requirements as defined in section 2.2.1.P.3.4 apply).

6.2.1.P.3.5 Process validation and/or evaluation

Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

6.2.1.P.4 Control of excipients

6.2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated. For excipients not described in one on of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre –fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

6.2.1.P.4.2 Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under 6.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

6.2.1.P.4.3 Validation of analytical procedures

Not applicable.

6.2.1.P.4.4 Justification of specifications

Not applicable.

6.2.1.P.4.5 Excipients of animal or human origin

Cf. Appendix 7.2.1. A.2.

6.2.1.P.4.6 Novel excipients

For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety. Information as indicated in section 3.2.S of the CTD should be provided in annex 2.1.A.3 (c.f. section 7.2.1.A.3) consistent with the respective clinical phase, details are to be included on e.g. their manufacturing process, characterisation and stability. If the same novel excipient is already described in the IMPD for the respective test product, cross-reference to the relevant section will suffice.

6.2.1.P.5 Control of the placebo product

6.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria. The specifications should at minimum include a test which enables to clearly differentiate between the respective investigational medicinal product and the placebo.

6.2.1.P.5.2 Analytical procedures

The analytical methods should be described for all tests included in the specification. It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General considerations).

6.2.1.P.7 Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the placebo in the clinical trial, should be stated.

6.2.1.P.8 Stability

The shelf-life and storage conditions of the placebo should be defined. The shelf life of the placebo product should preferably cover the anticipated duration of the clinical trial. Stability studies are only required in cases where there is reason to suspect that the placebo product will undergo changes in its

physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers, hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

7. Appendices

7.2.1.A.1 Facilities and equipment

Not applicable.

7.2.1.A.2 Adventitious agents safety evaluation

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

TSE agents

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

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

Viral safety

Where applicable, information assessing the risk with respect to potential viral contamination should be provided in this section. The risk of introducing viruses into the product and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated.

Other adventitious agents

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

7.2.1.A.3 Novel excipients

For novel excipients, information as indicated in section.3.2.S of the CTD should be provided, consistent with the respective clinical phase.

7.2.1.A.4 Solvents for reconstitution and diluents

For solvents for reconstitution and diluents, the relevant information as indicated in section 3.2.P of the CTD should be provided as applicable.

8. Auxiliary medicinal products

For auxiliary medicinal products the same requirements and principles apply as for investigational medicinal products. The requirements depend on the type of the product (authorised / not authorised / modified / non-modified medicinal product).

9. 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. Guidance given in this section relates only to changes that need to be notified to the competent authorities and when they should be notified.

The following examples of changes to IMP/auxiliary medicinal product quality data concerning:

- Importation of the medicinal product;
- Change of name or code of IMPs;
- Container closure system;
- Manufacturer(s) of drug substance;
- Manufacturing process of the drug substance;
- Specifications of active substance;
- Manufacturer(s) of medicinal product
- Manufacturing process of the medicinal product;
- Specification (release or shelf-life) of the medicinal product;
- Specification of excipients where these may affect product performance;
- Shelf-life including after first opening and reconstitution;
- Major change to the formulation;
- Storage conditions;
- Test procedures of active substance;
- Test procedures of the medicinal product; and
- Test procedures of non-pharmacopoeial excipients

are only to be regarded as “substantial” where they are likely to have a significant impact on:

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

In all cases, a modification is only to be regarded as “substantial” when one or more of the above criteria are met. The list is not exhaustive; a substantial modification might occur in some other aspect of a 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.

The modifications refer to the submitted IMPD. Should the changes be covered by the IMPD as submitted, a notification of a substantial modification will not be necessary.

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. Notifications of substantial modifications are only necessary for changes in ongoing clinical trials.

In the following table, examples are given for changes in IMPs, containing chemically defined or herbal drug substances, which should be notified as substantial modifications, and for changes, where a notification will not be necessary. This list does not claim to be exhaustive. The sponsor should decide on a case by case basis if a modification is to be classified as substantial or not.

Table 1

Changes in the quality	**Relevance for quality / safety?**		**Example**	
			Notification of a substantial modification	Notification of a substantial modification
	Yes	Possible	**not required**	**required**
Importation of the medicinal product		✓		Change of the importing site
Change of name or code of IMPs		✓		Change from company code to INN or trade name during ongoing clinical trial (exchange of the label)
Container closure system		✓	Change to a packaging material which is given as an alternative in the IMPD (e.g. blister –> HDPE- bottle)	New container closure system is introduced (e.g. less protective material, different container/material for diluted product)
Retest period for drug substance		✓	extension of retest period based on the scheme approved within the initial submission	Reduction of the retest period
Manufacturer(s) of drug substance.	✓		Alternate sites of manufacture within one company with unchanged specifications.	Change to a completely new manufacturer.

Table 2

Changes in the quality	Relevance for quality / safety?		Example	
			Notification of a substantial modification	Notification of a substantial modification
	Yes	Possible	**not required**	**required**
Manufacturing process of the drug substance.		✓	Change in the synthesis of an early step (prior to GMP Starting Material).	Different route of synthesis (final steps).
				Additional or new impurity[1].
			Modifications of the process parameters (same process, similar reagents).	Extension of the acceptance criteria.
				Changes in the physicochemical properties with influence on the quality of the IMP (e.g. particle size distribution, polymorphism etc.).
			Scale-Up.	
				Change in the manufacturing process of a herbal substance or herbal preparation.
Specifications of drug substance.		✓	Addition of test(s) (no safety reason)	Extension of the acceptance criteria.
			Tightening acceptance criteria (no safety reason)	Deletion of tests.
Manufacturer(s) of the medicinal product.		✓	Deletion of manufacturing, packaging or testing site (no safety reason).	Addition of manufacturing, packaging or testing sites
				Deletion of manufacturing, packaging or testing site (for safety reason, GMP non-compliance).
Manufacture of the medicinal product.		✓	Modifications of the process parameters (same process).	Significant changes to the manufacturing process (e.g. dry compacting vs. wet granulation, conventional granulation vs. fluid-bed-granulation).
			Scale-Up.	
Specification (release or shelf-life) of the medicinal product.		✓	Tightening of acceptance criteria (no safety reason).	Extension of acceptance criteria with clinical relevance, e.g. change in the hardness with influence on the disintegration time and/or the *in vitro*-dissolution.
			Addition of test(s) (no safety reason)	Deletion of tests.

[1] Extensions in the limits of single impurities should be toxicologically justified.

Table 3

Changes in the quality	Relevance for quality / safety?		Example	
			Notification of a substantial modification	Notification of a substantial modification
	Yes	Possible	**not required**	**required**
Specification of excipients, where these may affect product performance.	✓			E.g. changes in the particle size distribution with influence on the *in vitro*-dissolution.
Shelf-life of medicinal product including shelf life after first opening and reconstitution/dilution.		✓	Extension of shelf-life and/or extension of the storage conditions on the basis of additional data with unchanged shelf-life specifications, provided a proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing clinical trial, has been submitted with the initial or a previous substantial modification filing of the IMPD and has not been questioned by the competent authority (see 2.2.1.P.8 and similar sections).	Reduction of shelf-life, restriction of the storage conditions.
				Extension of shelf life - proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing clinical trial has not been submitted /approved with the initial filing of the IMPD.
Major change to the formulation.	✓		Qualitatively identical but quantitatively different composition of non-functional tablet coating.	Change in the composition (including exchange of excipients to excipients with same functional characteristics, e.g. disintegrant).
			Different form in an IR-tablet, e.g. round to capsule-shaped, with no clinical impact (e.g. the dissolution profile of the new form is comparable to the old one).	
Test methods of drug substance / drug product		✓	Variation of the method already covered by the IMPD.	New test methods (e.g. NIR instead of HPLC).
			The new test conditions are validated and lead to comparable or better validation results.	
Test methods of non-pharmacopoeial excipients.		✓	See above.	See above.
CoA for new batch of the medicinal product.		✓	New batch was manufactured using the approved process and manufacturing sites.	