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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

**GUIDELINE ON THE REQUIREMENTS TO THE CHEMICAL AND
PHARMACEUTICAL QUALITY DOCUMENTATION CONCERNING
INVESTIGATIONAL MEDICINAL PRODUCTS IN CLINICAL TRIALS**

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1. INTRODUCTION

1.1 Objectives of the Guideline

The following guideline is to be seen in connection with directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of the Good Clinical Practices in the conduct of clinical trials on medicinal products for human use, which came into force on May 1, 2004 and the pertaining document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” (ENTR/CT1). The latter describes the structure of the chemical-pharmaceutical data to be submitted in the Investigational Medicinal Product Dossier (IMPD), however provides no guidance on the required detail of information.

Since clinical trials will often be designed as multi-center 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 Community.

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 available is provided in this guideline.

1.2 Scope of the Guideline

This guideline addresses the documentation on the chemical and pharmaceutical quality of IMPs containing chemically defined active substances, synthetic peptides, 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 to be tested in phase I, phase II and phase III studies as well as the requirements for modified and unmodified comparator products and IMPs to be tested in generic bioequivalence studies. The section on authorised non-modified comparator products includes details on the extent of testing necessary to confirm their quality as required by Article 13 3(c) of Directive 2001/20/EC.

When compiling the quality part of the IMPD for phase II and phase III clinical studies, the larger and longer exposition 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 can not 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 active substance from the specific source to be used for an IMP is already included in a medicinal product authorised within the EU, not all the documentation outlined in the following chapters need to be submitted in the IMPD, but a simplified IMPD as described in the document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” (ENTR/CT1) 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 (The Rules Governing Medicinal Products in The European Community, Volume IV). The respective manufacturing licences should be presented, except in justified cases.

1.4 Submission of Data

In cases where an application for an authorisation for a clinical trial with the IMP in question has been previously submitted to the competent authority, the full documentation or alternatively only the revised documents may be provided. In any case an overview of changes to the documentation since the prior submission should be submitted. National requirements of the Member States should be taken into account, where applicable.

1.5 General Considerations

For IMPs to be used in clinical trials as described in chapters 2 to 4, 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 generic bioequivalence studies as described in chapter 5, reference to the Ph. Eur. should be made, where applicable.

2. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY CONCERNING INVESTIGATIONAL MEDICINAL PRODUCTS IN CLINICAL TRIALS

2.1.S DRUG SUBSTANCE

2.1.S.1 General Information

2.1.S.1.1 Nomenclature

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

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

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

2.1.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, chirality/stereochemistry as far as elucidated.

For radionuclide kits, the ligand's structural formula before and, if known, after the radio-labelling, should be given.

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

2.1.S.1.3 General Properties

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

The information may include, for example, melting point, polymorphism, solubility profile, pH- / pKa-values and hygroscopicity. Information about the particle size distribution should be provided, where relevant, e.g. to the pharmacokinetics of the drug substance.

For radionuclides, the nuclear and radiophysical properties should be stated.

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

The name(s) and address(es) of the manufacturer(s) as well as the site of production and batch release, if deviating, should be indicated. If appropriate, the name(s) and address(es) of the importer(s) should be indicated.

For radiopharmaceuticals, the manufacturer of the radionuclide, of radiolabelled precursors and of non-radioactive precursors should be stated.

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 reagents used should be provided. In case of critical steps in the synthesis, a more detailed description may be required.

The stereo-chemical properties of starting materials should be discussed, where applicable.

For radionuclides, the 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 organic-chemical precursors should be stated. For radiolabelled products, it may be necessary to give information on the consequences of an incomplete radiolabelling or of a possible *in vivo*-dissociation of the radiolabelled product.

For herbal substances or herbal preparations, a 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.

It should be documented if the manufacturing process 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 active substance used in the non-clinical studies should be presented.

The production scale or batch size should be stated.

2.1.S.3 Characterisation

2.1.S.3.1 Elucidation of Structure and other Characteristics

For chemical substances: a description of the methods used to determine the structure and of those used for further characterisation of the active substance (NMR, mass spectrometry, UV and IR spectra) should be provided. Typical spectra or other test results, as well as their interpretation, should be included in the documentation (e.g. copy of a DSC-run).

For radiopharmaceutical substances, the analogous non-radioactive substances should be used to determine the structure.

For herbal substances, details 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.

2.1.S.3.2 Impurities

For chemical substances: impurities, possible degradation products and residual solvents, deriving from the manufacturing process or starting materials relevant to the active substance used for the clinical trial, should be stated.

The consistency of impurity profiles between the active substance batches used in clinical trials, those used in non-clinical studies and those selected to establish the quality or the safety of the IMP should be demonstrated. The used solvents and catalysts should be taken into consideration. Deviations in the impurity profiles should be subject to risk assessment.

For radiopharmaceutical substances, the radionuclidic purity, the radiochemical purity and the chemical purity should be stated.

For herbal substances or herbal preparations, data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc. should be stated.

2.1.S.4 Control of the Drug Substance

2.1.S.4.1 Specifications

The specifications, the tests used as well as their acceptance criteria should be specified for the batch(es) of active substance(s) used in the clinical trial. Tests for identity and assay are mandatory. Preliminary 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 microbiological quality for active substances used in aseptically manufactured products should be specified.

For radiopharmaceutical substances, the radioactive concentration, the time of calibration and the half-life of the radio-active isotope should be specified.

Additional information for phase II and phase III clinical trials

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

2.1.S.4.2 Analytical Procedures

The analytical methods used for the active substance should be provided for all tests included in the specification (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, etc.).

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

2.1.S.4.3 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) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical procedures should be presented in a tabulated form. The methodology as described in the respective ICH guidelines should be applied.

Information for phase II clinical trials

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation carried out according to ICH-methodology 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.

Additional information for phase III clinical trials

In addition to the information to be provided for phase II clinical trials, a full validation report should be held available and should be submitted upon request.

2.1.S.4.4 Batch Analyses

Certificates of analyses or batch results for batches used in the non-clinical studies and, where applicable, for all batches used in previous clinical trials, should be supplied.

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

The manufacturing process used for each batch should be assigned as stated under 2.1.S.2.2. If differences occur, their possible influence on the safety of the IMP should be discussed. If available, this information should also be provided for the batches intended to be used in the planned clinical trial.

2.1.S.4.5 Justification of Specifications

It will be sufficient to briefly justify the specifications for impurities.

2.1.S.5 Reference Standards or Materials

The parameters characterising the batch of active substance established as primary reference standards should be presented, where applicable.

In addition, where applicable, information on how working standards for the determination of assay and impurities are generally established should be submitted.

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 generally known, a characterised herbarium sample should be available.

2.1.S.6 Container Closure System

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

2.1.S.7 Stability

The stability data available at the respective stage of development should be summarised in tables. The parameters critical for the stability of the active substance need to be presented, i.e. chemical and physical sensitivity. For herbal preparations, results of stress testing may be omitted, where justified.

2.1.P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

2.1.P.1 Description and Composition

The qualitative and quantitative composition of the IMP should be stated. A brief narrative description of the dosage form and the function of each excipient should be included.

In addition, the radioactivity per unit should be specified for radiopharmaceuticals.

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.

Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures should be demonstrated.

For radionuclide kits, the suitability of the method used for the radioactive radiolabelling for the intended use should be demonstrated (including results on the physiological distribution). For radionuclide generators, the suitability of the elution medium should be proven. For radiopharmaceuticals, it should be demonstrated that the intended radioactive concentration does not lead to radiolysis.

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.

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) of the manufacturing and control site(s) should be indicated. In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

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.

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

A flow chart of the successive steps, indicating the components used for each step, 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.

Additional information for phase II and phase III clinical trials

Changes in the current manufacturing process compared to the one used in phase I and phase II clinical trials, respectively, 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.

2.1.P.3.4 Control of Critical Steps and Intermediates

Data are not required at this stage, with the exception of

- non-standard manufacturing processes
- manufacturing processes for sterile products.

Additional information for phase III clinical trials

Critical manufacturing steps should be identified, their control as well as possible intermediates should be documented.

Should intermediates be stored, the duration of storage and the storage conditions should be given and justified.

2.1.P.3.5 Process Validation and/or Evaluation

Data are not required at this stage 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.

2.1.P.4 Control of Excipients

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 above pharmacopoeias, the specifications and certificates of analysis should be submitted.

2.1.P.4.2 Analytical Procedures

In cases where reference to a pharmacopoeial monograph listed under 2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

2.1.P.4.3 Validation of the Analytical Procedures

Not applicable.

2.1.P.4.4 Justification of Specifications

The specifications chosen for excipients not covered by a pharmacopoeial monograph listed under 2.1.P.4.1 should be justified.

2.1.P.4.5 Excipients of Animal or Human Origin

Cf. Appendix 2.1.A.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 the CTD-structure under 2.S. should be provided.

2.1.P.5 Control of the Investigational Medicinal Product

2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test procedures and acceptance criteria.

Preliminary upper limits may be set for both individual impurities and the sum of impurities. Safety considerations should be taken into account. The specifications should be reviewed and adjusted during further development.

For radiopharmaceuticals, it should be specified which tests are carried out prior to batch release and which tests are carried out retrospectively. For radionuclide kits, appropriate tests after radioactive radiolabelling should be stated.

Additional information for phase II and phase III clinical trials

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

2.1.P.5.2 Analytical Procedures

The analytical methods should be given for all tests included in the specification (e.g. dissolution test method).

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

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) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical procedures should be presented in a tabulated form. The methodology as described in the respective ICH guidelines should be applied.

Additional information for phase II clinical trials

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation, carried out according to ICH-methodology, 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.

Additional information for phase III clinical trials

In addition to the information to be provided for phase II clinical trials, a full validation report should be held available and should be submitted upon request.

2.1.P.5.4 Batch Analyses

Results or certificates of analysis for batches representative for the IMP to be used in the clinical study should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed (c.f.: attachment 1 of ENTR/CT1 “batch analysis and impurities”).

2.1.P.5.5 Characterisation of Impurities

The characterisation of impurities should be documented, if additional impurities not covered by section 2.1.S.3.2. are observed in the IMP.

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 for impurities. Toxicological justification should be given, where appropriate.

Additional information for phase II and phase III clinical trials

The choice of specifications should be briefly justified. Changes compared to previous specifications should be explained. Toxicological justification should be given, where appropriate.

2.1.P.6 Reference Standards or Materials

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

In addition, where applicable, data on the establishment of the working standards for assay and impurities, used for testing the batches described in section 2.1.P.5.4 - Batch Analyses – should be provided.

Section 2.1.S.5 - Reference Standards or Materials - may be referred to where applicable.

2.1.P.7 Container Closure System

The intended packaging for the IMP to be used in the clinical trial as well as that for solvents and diluents, where applicable, should be stated. If non-compendial materials are used, a description and specifications should be provided.

2.1.P.8 Stability

The shelf life of the product should preferably cover the anticipated duration of the clinical trial. Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical trial and throughout its entire duration. A respective stability commitment should be given, where applicable.

For preparations intended for multiple applications after reconstitution, dilution or mixing, in-use stability data should be presented. These studies are not required if the preparation is to be used immediately after opening or reconstitution 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. Any 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 study 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 study should be provided. Data should include results from studies under accelerated and long-term storage conditions.

3. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF AUTHORISED MODIFIED COMPARATOR PRODUCTS IN CLINICAL TRIALS

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

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

2.1.P MODIFIED COMPARATOR PRODUCT

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 substances 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.

2.1.P.2 Pharmaceutical Development

The modifications carried out on the authorised comparator 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.

In case of solid oral dosage forms, comparative dissolution profiles of both original and modified comparator product should be provided to ensure unchanged bio-pharmaceutical properties (c.f. “Note for Guidance on Bioavailability and Bioequivalence, annex II, Dissolution Testing” for demonstrating similarity of dissolution profiles). In those cases

where equivalence cannot be established in vitro, additional clinical data to support equivalence may be necessary.

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) of the manufacturing and control site(s) and batch release should be indicated. In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

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.

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, stating the applied limits.

2.1.P.4 Control of Excipients

All excipients that are used to modify the authorised product should be indicated.

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 above pharmacopoeias, the specifications and certificates of analysis should be provided.

2.1.P.4.2 Analytical Procedures

In cases where reference to a pharmacopoeial monograph listed under 2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

2.1.P.4.5 Excipients of Animal or Human Origin

Cf. Appendix 2.1.A.2.

2.1.P.5 Control of the Modified Comparator Product

2.1.P.5.1 Specifications

The release and shelf-life specification(s) for the modified comparator product, including their justification and pertaining analytical procedures, should be provided. Generally, they should include description and identification of the active substance as well as the control of important pharmaceutical and technological properties, such as dissolution. Depending on the degree of modification of the authorised product, additional quality criteria, e.g. determination of the active substance(s) and impurities/degradants, may need to be tested and specified.

2.1.P.5.2 Analytical Procedures

The analytical methods should be given. For parameters relevant to the performance of the comparator product, e.g. dissolution, the methods should be described.

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 procedures, carried out according to ICH-methodology, 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.

2.1.P.5.4 Batch Analyses

Results or certificates of analysis for the modified comparator product to be used in the clinical trial should be provided.

2.1.P.5.5 Characterisation of Impurities

In those cases, where the comparator product has undergone major modification by the sponsor 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 comparator 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. This is not required for authorised products which are only re-packaged.

2.1.P.7 Container Closure System

The type of packaging, material and package size(s) should be specified. If materials other than those authorised are used, a description and specifications should be provided.

2.1.P.8 Stability

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

A minimum of stability data on the modified comparator 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 study should be provided.

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

4. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF AUTHORISED, NON-MODIFIED TEST AND COMPARATOR PRODUCTS IN CLINICAL TRIALS

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

Information on the analytical methods needed for at least reduced testing (e.g. identity) should be provided. The relevant analyses, tests or checks necessary to confirm quality as required

by Article 13 3(c) of directive 2001/20/EC shall therefore be based on proof of existence of the equivalent of a marketing authorisation, combined with identity testing.

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

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

5. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS IN GENERIC BIO-EQUIVALENCE STUDIES (CHEMICAL SUBSTANCES)

IMPs to be used in generic bio-equivalence studies supporting EU-licensing activities should meet Ph. Eur. requirements.

2.1.S DRUG SUBSTANCE

2.1.S.1 General information

2.1.S.1.1 Nomenclature

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

2.1.S.1.2 Structure

The structural formula should be presented.

2.1.S.1.3 General Properties

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

2.1.S.2 Manufacture

2.1.S.2.1 Manufacturer(s)

The name(s) and address(es) of the manufacturer(s) as well as the site of production, quality control and batch release, if deviating, should be indicated. If appropriate, the name(s) and address(es) of the importer(s) should be indicated.

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

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, or, in the absence of such a monograph, USP or JP, no further details are required.

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.

2.1.S.3 Characterisation

2.1.S.3.2 Impurities

For substances which comply with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, or, in the absence of such a monograph, USP or JP, no further details are required.

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

2.1.S.4 Control of the Drug Substance

2.1.S.4.1 Specifications

The microbiological quality of active 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, or, in the absence of such a monograph, USP or JP, no further details are required.

In cases where reference to a pharmacopoeial monograph listed above cannot be made, specifications, tests used as well as the acceptance criteria should be specified for the batch(es) of the active substance(s) intended for use in the bio-equivalence study.

2.1.S.4.2 Analytical Procedures

For substances for which reference to a pharmacopoeial monograph listed under S.1.S.4.1 of this chapter cannot be made, the analytical methods used for the active substance (e.g. reverse-phase-HPLC, potentiometric titration, head-space-GC, etc.) should be provided.

2.1.S.4.3 Validation of Analytical Procedures

For substances for which reference to a pharmacopoeial monograph listed under S.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 ICH-conforming validation of the analytical procedures should be provided (e.g. values found for repeatability, limit of quantification etc.). A full validation report should be held available for submission upon request.

2.1.S.4.4 Batch Analyses

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

2.1.S.4.5 Justification of Specifications

For substances for which reference to a pharmacopoeial monograph listed under S.1.S.4.1 of this chapter cannot be made, it will be sufficient to provide a brief justification of the specifications of impurities.

2.1.S.5 Reference Standards or Materials

For substances for which reference to a pharmacopoeial monograph listed under S.1.S.4.1 of this chapter cannot be made, the parameters characterising the batch of active substance established as primary reference standards should be presented.

Information on how working standards for the determination of assay and impurities are generally established should be submitted.

2.1.S.6 Container Closure System

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

2.1.S.7 Stability

The available stability data should be provided in a tabulated form.

2.1.P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

2.1.P.1 Description and Composition

The qualitative and quantitative composition of the IMP should be stated.

2.1.P.2 Pharmaceutical Development

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

2.1.P.3 Manufacture

2.1.P.3.1 Manufacturer(s)

The name(s) and address(es) of the manufacturing and control site(s) should be indicated. In case multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities in the manufacturing chain should be clearly indicated.

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.

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, should be provided. In addition, a brief narrative description of the manufacturing process should be included.

2.1.P.3.4 Control of Critical Steps and Intermediates

Critical manufacturing steps should be identified, their control as well as possible intermediates should be stated.

2.1.P.3.5 Process Validation and/or Evaluation

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

2.1.P.4 Control of Excipients

2.1.P.4.1 Specifications

References to the Ph. Eur., the pharmacopoeia of an EU Member State, or, in the absence of such a monograph, USP or JP, should be indicated. For excipients not described in one of the above pharmacopoeias, the specifications should be provided.

2.1.P.4.2 Analytical procedures

In cases where reference to a pharmacopoeial monograph listed under 2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

2.1.P.4.5 Excipients of Animal or Human Origin

C. f. Appendix 2.1.A.2.

2.1.P.4.6 Novel Excipients

For novel excipients, details on the manufacturing process, characterisation and control as well as concerning product safety are to be provided. Information as indicated in the CTD-structure under 2.S. should be provided.

2.1.P.5 Control of the Investigational Medicinal Product

2.1.P.5.1 Specifications

The chosen release and shelf-life specifications should be submitted, including test procedures and acceptance criteria.

2.1.P.5.2 Analytical Procedures

The analytical methods should be given. For parameters relevant to the performance of the comparator product, e.g. dissolution, the methods should be described.

2.1.P.5.3 Validation of Analytical Procedures

The validation of the analytical procedures should be performed in accordance with the respective ICH guidelines. A tabulated summary of the validation results should be provided. A full validation report should be held available for submission upon request.

2.1.P.5.4 Batch Analyses

Certificates of analysis for the batch(es) intended to be used in the planned bio-equivalence study should be provided.

The batch number, batch size, manufacturing site, manufacturing date, control methods, where applicable importing site, acceptance criteria, the test results, batch release site, location of reference and witness samples used should be listed as well as the batch number of the active substance used and the date of analysis.

2.1.P.5.5 Characterisation of Impurities

Impurities should be documented if they differ from the description in section 2.1.S.3.2. of this chapter.

2.1.P.5.6 Justification of Specification(s)

The choice of specifications should be briefly justified.

2.1.P.6 Reference Standards or Materials

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

Data on the establishment of the working standards for assay and impurities, used for testing the batches described in section 2.1.P.5.4 - Batch Analyses – of this chapter should be provided.

Section 2.1.S.5 - Reference Standards or Materials - of this chapter may be referred to, where applicable.

2.1.P.7 Container Closure System

The packaging to be used for the IMP in the clinical trial should be stated.

2.1.P.8 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 bio-equivalence study should be provided. Data should at least include results from studies under accelerated and long-term storage conditions.

6. APPENDICES

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. CHANGES TO THE INVESTIGATIONAL MEDICINAL PRODUCT WITH A NEED TO REQUEST A SUBSTANTIAL AMENDMENT TO THE IMPD

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

The following changes to IMP quality data concerning

- Importation of the medicinal product
- Change of name or code of IMPs
- Immediate packaging material
- Manufacturer(s) of active substance
- Manufacturing process of the active substance
- Specifications of active substance
- Manufacture 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
- 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.

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

When an amendment 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. Notification of substantial amendments 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 active substances, which should be notified as substantial amendments, and for changes, where a notification will not be necessary. This list does not claim to be exhaustive. The sponsor should check on a case by case basis if an amendment is to be classified as substantial or not.

ENTR/CT 1 Attachment 5	Relevance for quality / safety?		Example	
	Yes	Possible	Notification of a substantial amendment not required	Notification of a substantial amendment required
Changes in the quality				
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 study (exchange of the label)
Immediate packaging material		●	Change to a packaging material which is given as an alternative in the IMPD (e.g. blister -> HDPE-bottle)	Immediate packaging material
Manufacturer(s) of active substance	●		Alternate sites of manufacture within one company with unchanged specifications	Change to a completely new manufacturer
Manufacturing process of the active substance		●	Change in the synthesis of an early step (prior to GMP Starting Material) Modifications of the process parameters (same process, same reagents) Scale-Up	different route of synthesis (final steps) Additional or new impurity ¹ Extension of the acceptance limits Changes in the physicochemical properties with influence on the quality of the IMP (e.g. particle size distribution, polymorphism etc.) Change in the manufacturing process of a herbal substance or herbal preparation

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

ENTR/CT 1 Attachment 5	Relevance for quality / safety?		Example	
	Yes	Possible	Notification of a substantial amendment not required	Notification of a substantial amendment required
Changes in the quality				
Specifications of active substance		●		Extension of the acceptance limits Deletion of tests
Manufacture of the medicinal product		●	Modifications of the process parameters (same process) Scale-Up	Significant changes to the manufacturing process (e.g. dry compacting → wet granulation, conventional granulation → Fluid-bed-granulation)
Specification (release or shelf-life) of the medicinal product		●		Extension of the acceptance limits with clinical relevance, e.g. Change in the hardness with influence on the disintegration time and/or the in vitro-dissolution Deletion of tests
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 including after first opening and reconstitution		●	Extension of shelf-life, extension of the storage conditions on the basis of additional data with unchanged shelf-life specifications	Reduction of shelf-life, restriction of the storage conditions

ENTR/CT 1 Attachment 5	Relevance for quality / safety?		Example	
Changes in the quality	Yes	Possible	Notification of a substantial amendment not required	Notification of a substantial amendment required
Major change to the formulation	●		Qualitatively identical but quantitatively different composition of non-functional tablet coating Different form in an IR-tablet	Change in the composition (including exchange of excipients to excipients with same functional characteristics, e.g. disintegrant)
Test procedures of active substance		●	Variation of the method already covered by the IMPD The new test conditions are validated and lead to comparable or better validation results	New test methods (e.g. NIR instead of HPLC)
Test procedures of the medicinal product		●		
Test procedures of non-pharmacopoeial excipients		●		

APPENDIX: GENERAL REQUIREMENTS

The following table provides general guidance on the information required for the different phases of clinical trials. Details on the specific requirements for the different chapters of the IMPD is given in chapters 2 to 6.

	Phase 1	Phase 2	Phase 3
2.1.S			
<i>Drug Substance</i>			
2.1.S.1 General Information			
2.1.S.1.1 Nomenclature	X	X	X
2.1.S.1.2 Structure	X	X	X
2.1.S.1.3 General Properties	X	X	X
2.1.S.2 Manufacture			
2.1.S.2.1 Manufacturer(s)	X	X	X
2.1.S.2.2 Description of Manufacturing Process and Process Controls	X Brief summary and flow chart.	X Brief summary and flow chart.	X Brief summary and flow chart.
2.1.S.3 Characterisation			
2.1.S.3.1	X	X	X

	Phase 1	Phase 2	Phase 3
Elucidation of Structure and other Characteristics			
2.1.S.3.2 Impurities	X	X	X
2.1.S.4 Control of Drug Substance			
2.1.S.4.1 Specification	X At least batch results.	X Preliminary specifications.	X Specifications.
2.1.S.4.2 Analytical Procedures	X Analytical methods.	X Analytical methods.	X Analytical methods.
2.1.S.4.3 Validation of Analytical Procedures	X Table of acceptance limits for validation.	X Tabulated summary of results.	X Validation report to be held available.
2.1.S.4.4 Batch Analyses	X All batches used so far.	X Current batch(es).	X Current batch(es).
2.1.S.4.5 Justification of Specification	X	X	X
2.1.S.5 Reference Standards or Materials	X Limited information on primary reference standard and working standards, where applicable.	X Limited information on primary reference standard and working standards, where applicable.	X Limited information on primary reference standard and working standards, where applicable.
2.1.S.6 Container Closure System	X Brief description.	X Brief description.	X Brief description.

	Phase 1	Phase 2	Phase 3
2.1.S.7 Stability	X Tabulated summary of available data.	X Tabulated summary of available data.	X Tabulated summary of available data.
2.1.P <i>Medicinal Product</i>			
2.1.P.1 Description and Composition of the Medicinal Product	X	X	X
2.1.P.2 Pharmaceutical Development	X Short description, where applicable.	X Brief summary, taking into account changes of clinical relevance.	X Summary taking, into account changes of clinical relevance.
2.1.P.3 Manufacture			
2.1.P.3.1 Manufacturer(s)	X	X	X
2.1.P.3.2 Batch Formula	X	X	X
2.1.P.3.3 Description of Manufacturing Process and Process Controls	X Brief description and flowchart.	X Description and flowchart, taking into account changes of clinical relevance.	X Description and flowchart, taking into account changes of clinical relevance.
2.1.P.3.4 Controls of Critical Steps and Intermediates	X Provide data for non-	X Provide data for non-	X Control of critical steps

	Phase 1	Phase 2	Phase 3
	standard processes and the manufacture of sterile products.	standard processes and the manufacture of sterile products.	and intermediates.
2.1.P.3.5 Process Validation and Evaluation	X For non-standard sterilisation processes.	X For non-standard sterilisation processes.	X For non-standard sterilisation processes.
2.1.P.4 Control of Excipients			
2.1.P.4.1 Specifications	X If non-compendial	X If non-compendial.	X If non-compendial.
2.1.P.4.2 Analytical Procedures	X Brief description, if non-compendial.	X Brief description, if non-compendial.	X Brief description, if non-compendial.
2.1.P.4.3 Validation of Analytical Procedures	-	-	-
2.1.P.4.4 Justification of Specifications	X If non-compendial.	X If non-compendial.	X If non-compendial.
2.1.P.4.5 Excipients of Human or Animal Origin	X Cf. Appendix 2.1.A.2.	X Cf. Appendix 2.1.A.2.	X Cf. Appendix 2.1.A.2.
2.1.P.4.6 Novel Excipients	X 2.S.1 applies.	X 2.S.1 applies.	X 2.S.1 applies.
2.1.P.5 Control of Medicinal Product			

	Phase 1	Phase 2	Phase 3
2.1.P.5.1 Specifications	X At least batch results.	X Preliminary specifications.	X Specifications.
2.1.P.5.2 Analytical Procedures	X Analytical methods.	X Analytical methods.	X Analytical methods
2.1.P.5.3 Validation of Analytical Procedures	X Table of acceptance limits for validation.	X Tabulated summary of results.	X Validation report to be held available.
2.1.P.5.4 Batch Analyses	X Representative batches.	X Representative batches.	X Representative batches
2.1.P.5.5 Characterisation of Impurities	X Additional information, if not given in API section.	X Additional information, if not given in API section.	X Additional information, if not given in API section.
2.1.P.5.6 Justification of Specification(s)	X Brief justification for impurities.	X Brief justification, taking into account changes of clinical relevance.	X Brief justification, taking into account changes of clinical relevance.
2.1.P.6 Reference Standards or Materials	X Limited information on primary reference standard and working standards, where applicable.	X Limited information on primary reference standard and working standards, where applicable.	X Limited information on primary reference standard and working standards, where applicable.

	Phase 1	Phase 2	Phase 3
2.1.P.7 Container Closure System	X Description.	X Description.	X Description.
2.1.P.8 Stability	X Tabulated summary of available data.	X Tabulated summary of available data.	X Tabulated summary of available data.
2.1.A Appendices	Phase 1	Phase 2	Phase 3
2.1.A.2 Adventitious Agents Safety Evaluation	Where relevant	Where relevant	Where relevant