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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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7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.eu.int http://www.emea.eu.int

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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 European Commission document "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial" in its current version. 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-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 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 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 containing chemically defined drug 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 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 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 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 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" 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).

1.4 Submission of Data

In addition to the numeration given in the Commission document, “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” the headings of the Guideline are preceded by an additional Arabic number to facilitate the Guideline’s use. However, the numbering in the IMPD should follow the numbering given in the Commission document. The above mentioned preceding number should be omitted in the documentation.

1.5 General Considerations

For IMPs to be used in clinical trials as described in chapters 2 to 6, 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.

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 1” 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.

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

2.2.1.S.1 General Information:

2.2.1.S.1.1 Nomenclature

Information concerning the nomenclature of the drug substance (e.g. proposed INN-name, 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 radionuclide or the radio-labelled substance should be stated additionally.

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

In the case of radionuclide generators, both parent radionuclide and daughter radionuclide are considered as drug substances. For kits, which are to be radio-labelled, the part of the formulation which will carry or bind the radionuclide 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, 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.

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 production 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.

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. 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 with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP, no further details are required.

For radio-nuclides, 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 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.

The production scale or range of batch sizes to be used in the clinical trial should be stated.

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 conrol or control of a precursor to a potential genotoxic impurity..

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.

2.1.2.S.3 Characterisation:

2.1.2.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 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.

2.1.2.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.

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

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 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. 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 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 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, potentiometric titration, head-space-GC, 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

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.

2.2.1.S.4.4 Batch Analyses

Certificates of analyses or batch results for batches used in the current clinical trial, in the non-clinical studies and, where applicable, for all batches used in previous clinical trials, should be supplied. If these data are not available for the batches to be used in the current clinical trial, data for representative batches may be submitted instead.

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 2.2.1.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.

2.2.1.S.7 Stability:

The stability data available at the respective stage of development should be summarised in tables. 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.

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 qualitative and quantitative composition of the IMP should be stated. A short statement or a tabulation of the dosage form and the function of each excipient should be included.

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

2.2.1.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 extemporaneously prepared medicinal products, e.g. 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.

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 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.

2.2.1.P.2.3 Manufacturing Process Development

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.

2.2.1.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 production site involved in manufacture 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.

When packaging is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at that institution, and where an exemption from the need to hold a manufacturing authorisation, as provided for in Art. 9.2 of Directive 2005/28/EC 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
- manufacturing processes for sterile products.

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 and non-standard manufacturing processes. In these cases, 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.

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.

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.

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 extemporaneously prepared medicinal products, 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).

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

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 “batch analysis and impurities” of EU-Commission document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities….” in its current version).

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.

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 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 of the IMP should be defined based on the stability profile of the active substance and the available data on the IMP. Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical studies and throughout its entire duration. This should include the proposal for shelf-life extension, defining the criteria based on which the sponsor will extend the shelf-life during an ongoing study. A stability commitment should be provided. 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.

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. 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, 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 following chapter.

For products sourced from those countries outside the EU/EEA mentioned in the first paragraph, information on the analytical methods needed for at least reduced testing (e.g. identity) should be provided. The relevant analyses, tests or checks necessary to confirm quality as required by Article 13

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

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

For IMPs sourced from outside of the EU/EEA, MRA-partner countries or ICH regions, a full documentation, 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 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 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 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 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. 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 production site involved in the modification 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.

When packaging is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at that institution, and where an exemption from the need to hold a manufacturing authorisation, as provided for in Art. 9.2 of Directive 2005/28/EC 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.

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 Comparator Product:

4.2.1.P.5.1 Specifications

The chosen release and shelf-life specifications of the modified comparator 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 comparator product, e.g. dissolution, the methods should be described.

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 comparator product to be used in the clinical trial or of a representative batch 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 “batch analysis and impurities” of EU-Commission document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities….” in its current version).

4.2.1.P.5.5 Characterisation of Impurities

In those cases, where the comparator 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 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 (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 comparator 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.

4.2.1.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.

In the case of a significant modification, e.g. grinding of a tablet, re-lubrication and compression, or processing with an excipient hitherto not present in the formulation with a likely impact on product stability, 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. Any degree of extrapolation may not exceed the shelf-life originally assigned to the specific batch of authorised product by its MAH.

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

5. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS CONTAINING EXISTING ACTIVE SUBSTANCES 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 1" 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.

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

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, 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 production 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 with a monograph of the Ph. Eur., the pharmacopoeia of an EU Member State, 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.

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.

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 drug substance used for the bio-equivalence study should be stated.

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.

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, potentiometric titration, head-space-GC, 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.

5.2.1.S.7 Stability:

The available stability data should be provided in a tabulated form. Alternatively, confirmation that the active substance will meet specifications at time of use will be acceptable.

5.2.1.P INVESTIGATIONAL MEDICINAL PRODUCT UNDER TEST

5.2.1.P.1 Description and Composition:

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

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 production site involved in manufacture 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.

When packaging is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at that institution, and where an exemption from the need to hold a manufacturing authorisation, as provided for in Art. 9.2 of Directive 2005/28/EC 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.

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 and non-standard manufacturing processes. In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described (c.f. Annex II to Note for Guidance on Process Validation: Non-Standard Processes (CPMP/QWP/2054/03).

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.

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.

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).

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 (c.f.: attachment 1 “batch analysis and impurities” of EU-Commission document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities….” in its current version).

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 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 qualitative and quantitative composition of the placebo should be stated. 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 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 production site and facility involved in manufacture 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 packaging is carried out at a hospital, health centre or clinic where the investigational medicinal product is to be used for the trial exclusively at that institution, and where an exemption from the need to hold a manufacturing authorisation, as provided for in Art. 9.2 of Directive 2005/28/EC 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.

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.

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 these cases, 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.

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.

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 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. 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 examples of changes to IMP quality data concerning

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

In all cases, an amendment is only to be regarded as “substantial” when one or more of the above criteria are met. The list is not exhaustive; a substantial amendment might occur in some other aspect of a clinical trial (cf. European Commission document “Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial” in its current version) .

Assessment of an IMPD should be focussed on patient safety. Therefore, any amendment involving a potential new risk has to be considered a substantial amendment. This may be especially the case for changes in impurities, microbial contamination, viral safety, TSE and in some particular cases to stability when toxic degradation products may be generated.

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. Notifications 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 drug 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 decide on a case by case basis if an amendment is to be classified as substantial or not.

"Detailed guidance for the request for authorisation …." 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**
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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.eu.int http://www.emea.eu.int

"Detailed guidance for the request for authorisation …." 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**
Manufacturer(s) of drug substance	●		Alternate sites of manufacture within one company with unchanged specifications	Change to a completely new manufacturer
Manufacturing process of the drug 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 criteria 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
Specifications of drug substance		●		Extension of the acceptance criteria 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		●	Tightening of specifications	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 Deletion of tests

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

"Detailed guidance for the request for authorisation …." 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**
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 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 study, has been submitted with the initial 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
Major change to the formulation	●		Qualitatively identical but quantitatively different composition of non-functional tablet coating Different form in an IR-tablet, e.g. round to capsule-shaped	Change in the composition (including exchange of excipients to excipients with same functional characteristics, e.g. disintegrant)
Test methods of drug 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 methods of the medicinal product		●	see above	see above
Test methods of non-pharmacopoeial excipients		●	see above	see above