الهيئة العامة للغذاء والدواء
Saudi Food & Drug Authority

Guidelines for Chemical and Pharmaceutical Quality Documentation of Small Molecules Investigational Products in Clinical Trials

Adopted from EMA and edited by SFDA

Version 1.0

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Saudi Food & Drug Authority

Drug Sector

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Saudi Food and Drug Authority

Vision and Mission

Vision

To be a leading international science-based regulator to protect and promote public health

Mission

Protecting the community through regulations and effective controls to ensure the safety of food, drugs, medical devices, cosmetics, pesticides and feed

Document Control

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1. INTRODUCTION

This guideline is adopted from the European Medicines Agency (EMA) “Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials”.

1.1 Objective

This guideline outlines the required documentation for the chemical and pharmaceutical quality of investigational product (IP) dossiers for small molecules. It covers chemically defined drug substances, synthetic peptides, herbal substances, herbal preparations, and chemically defined radioactive/radiolabeled substances that must be submitted to the Saudi Food and Drug Authority (SFDA)for approval before initiating clinical trials in humans

1.2 Scope

This guideline specifies the documentation required for the chemical and pharmaceutical quality of small-molecule investigational products (IP) dossiers submitted to the Saudi Food and Drug Authority (SFDA) for clinical trial approval. It applies to the following:

- Chemically defined drug substances
- Herbal substances and preparations
- Chemically defined radioactive/radiolabeled substances

1.3 General points concerning all IPs

IPs should be produced in accordance with the principles and the detailed SFDA guidelines of Good Manufacturing Practices (GMP) for Medicinal Products.

1.4 Submission of data

The IPD should be provided in a clearly structured format following the numbering system outlined in the Chapters 2 to 8 of this Guideline. However, the first Arabic number being introduced only to facilitate the Guideline’s use should be omitted in the dossier. The IPD should include the most up-to-date information relevant to the clinical trial available at the time of CTA submission. .

1.5 General considerations

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

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

For impurities in IPs, 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.

1.6 Labeling and Packaging Requirements:

The labeling and packaging of IPs should follow the SFDA IP Labeling and Packaging Memo.

1.7 Regional Administrative Information

1.7.1 Alcohol-content declaration

This section shall contain a declaration letter stating that the investigational product is free from alcohol. In the case of alcohol present in the investigational product, a pre-approval from the authority is required along with the justification to make it possible for the authority to evaluate the request and send the response to the applicant.

1.7.2 Pork-content declaration

This section shall contain a declaration letter stating that the investigational product is free from any materials of pork/porcine source.

2. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY CONCERNING INVESTIGATIONAL 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 shall follow the requirements described in the 'SFDA Drug Master File (DMF): Guidance for Submission".

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

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

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

2.2.1.S.1 General information

2.2.1.S.1.1 Nomenclature

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

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

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

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

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

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

2.2.1.S.1.3 General properties

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

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

2.2.1.S.2 Manufacture

2.2.1.S.2.1 Manufacturer(s)

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

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

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

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

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

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

2.2.1.S.2.3 Control of materials

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

2.2.1.S.2.4 Control of critical steps and intermediates

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

2.2.1.S.2.5 Process validation and/or evaluation

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

2.2.1.S.2.6 Manufacturing process development

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

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

2.2.1.S.3 Characterisation

2.2.1.S.3.1 Elucidation of structure and other characteristics

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

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

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

Where applicable, details should be given on the biological activity.

2.2.1.S.3.2 Impurities

For substances which comply with a monograph of the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been discussed.

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

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

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

In the case of radio-nuclides or radio-labelled substances which are used in phase I studies in humans to develop a non-radioactive medicinal product, the radiochemical purity and the chemical purity should be indicated describing any assumptions made, e.g. as a consequence of the determination being made prior to dilution with cold material. For radiopharmaceutical substances, the radio-nuclidic purity, the radiochemical purity and the chemical purity should be stated and discussed.

For herbal substances or herbal preparations, data on potential contamination by micro-organisms, products of micro-organisms, aflatoxins, pesticides, toxic metals, radioactive

contamination, fumigants, etc. should be stated. The general requirements of the Ph. Eur. should be fulfilled.

2.2.1.S.4 Control of the Drug Substance

2.2.1.S.4.1 Specification(s)

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

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

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

For substances which comply with United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, reference to the relevant monograph will be sufficient, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvent or catalyst.

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

Additional information for phase II and phase III clinical trials

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

2.2.1.S.4.2 Analytical procedures

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

FID, etc.). It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter 1.5 General Considerations).

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

For substances which comply with a monograph of United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, reference to the relevant monograph will be sufficient.

2.2.1.S.4.3 Validation of analytical procedures

Information for phase I clinical trials

The suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form.

Information for phase II and III clinical trials

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation carried out should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

For substances which comply with a monograph of the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, reference to the relevant monograph will be sufficient.

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

2.2.1.S.4.4 Batch analyses

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

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

2.2.1.S.4.4 Justification of specification(s)

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

2.2.1.S.5 Reference standards or materials

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

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

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

2.2.1.S.6 Container closure system

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

2.2.1.S.7 Stability

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

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

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

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

2.2.1.P Investigational product under test

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

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

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

2.2.1.P.2 Pharmaceutical development

A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided. For early development, there may be no or only limited information to include in this section.

The new drug components, the dosage form and the administration device if any should be safe and suitable for the patient population. Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures should be demonstrated. For products to be reconstituted or diluted prior to their use, the method of preparation should be summarised and reference made to a full description in the clinical protocol or associated handling instructions which will be available at the clinical site should be provided.

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

Additional information for phase II and phase III clinical trials

If changes in the formulation or dosage form compared to the IP used in earlier clinical trials have been made, the relevance of the earlier material compared to the drug under testing should

be described. Special consideration should be given to dosage form specific changes in quality parameters with potential clinical relevance, e.g. in vitro dissolution rate.

2.2.1.P.2.1 Manufacturing process development

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

2.2.1.P.3 Manufacture

2.2.1.P.3.1 Manufacturer(s)

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

When re-packaging and or re-labelling is carried out at a hospital, health center or clinic where the IP is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

2.2.1.P.3.2 Batch formula

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

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

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

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

2.2.1.P.3.4 Controls of critical steps and intermediates

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

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

For sterilisation by filtration the maximum acceptable bioburden prior to the filtration must be stated in the application. In most situations NMT 10 CFU/100 ml will be acceptable, depending on the volume to be filtered in relation to the diameter of the filter. If this requirement is not met, a pre-filtration through a bacteria-retaining filter should be carried out in order to obtain a sufficiently low bioburden. If availability of the formulated new drug is limited, a prefiltration/filtration volume of less than 100 ml may be tested if justified.

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

Additional information for phase III clinical trials

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

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

2.2.1.P.3.5 Process validation and/or evaluation

Data are not required during the development phases, i.e. clinical phases I to III, except for non- standard sterilization processes not described in the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

2.2.1.P.4 Control of excipients

2.2.1.P.4.1 Specifications

References to the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia should be indicated. For excipients not described

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

2.2.1.P.4.2 Analytical procedures

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

2.2.1.P.4.3 Validation of the analytical procedures

Not applicable.

2.2.1.P.4.4 Justification of specifications

Not applicable.

2.2.1.P.4.5 Excipients of animal or human origin

Cf. section 7.2.1. A.2.

2.2.1.P.4.6 Novel excipients

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

2.2.1.P.5 Control of the investigational product

2.2.1.P.5.1 Specifications

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

Upper limits may be set for both individual degradation products and the sum of degradation products. Safety considerations should be taken into account. The limits should be supported

by the impurity profiles of batches of active substance used in non-clinical/clinical studies. The specifications and acceptance criteria should be reviewed and adjusted during further development.

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

The omission of drug product specific tests should be justified.

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

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

Additional information for phase II and phase III clinical trials

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

2.2.1.P.5.2 Analytical procedures

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

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

2.2.1.P.5.3 Validation of analytical procedures

For phase I clinical trials, the suitability of the analytical methods used should be confirmed. The acceptance limits (e.g. acceptance limits for the determination of the content of impurities, where relevant) and the parameters (specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate) for performing validation of the analytical methods should be presented in a tabulated form.

Additional information for phase II and III clinical trials

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of the validation should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

2.2.1.P.5.4 Batch analyses

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

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

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

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

2.2.1.P.5.5 Characterisation of impurities

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

Additional information for phase II and phase III clinical trials

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

2.2.1.P.6 Reference standards or materials

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

2.2.1.P.7 Container closure system

The intended immediate packaging and additionally, where relevant for the quality of the drug product, the outer packaging to be used for the IP in the clinical trial, should be stated. Where appropriate, reference should be made to the relevant pharmacopoeial monograph. If the drug 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. parenteral, ophthalmic products, oral solutions), more details may be needed for phase III studies (e.g. extractables, leachable). For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

If a medical device is to be used for administration its regulatory status should be explicitly stated. In the absence of certification for its intended purpose, a statement of compliance of the medical device with relevant legal requirements for safety and performance is required. Where a new drug is combined with an integral medical device and the principal mechanism of action is that of the new drug, the combined product is governed by the medicine's legislation.

2.2.1.P.8 Stability

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

- Results at long-term as well as at accelerated storage conditions are available;

- No significant changes in stability behavior are observed. If any observed, justification should be provided;
- Stability protocol covering the proposed extrapolated shelf life should be provided;
- Criteria used to extrapolate data should be clearly defined; and
- Depending on the data available:
  - A fourfold extrapolation of accelerated stability data may be acceptable up to a shelf life of 12 months
  - An extrapolation of + max 12 months to long-term stability data available (at least 6- months) may be acceptable for a shelf life of more than 12 months
  - Other schemes may be possible but should be justified.

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

In case the drug product is stored in a bulk for a significant time period, relevant stability data should be provided as well as shelf life, storage conditions and packaging material for the bulk.

In case the final drug product shelf life is calculated not from the first mixing of the drug substance with excipients but from the time of packaging into the primary package, this should be clearly stated and justified.

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

For preparations intended for applications after reconstitution, dilution or mixing, and products in multi-dose containers, excluding oral solid dosage forms, in-use stability data should be presented. In- use stability studies should cover the practice described in the clinical protocol. Relevant parameters should be monitored within the in-use stability studies (e.g. appearance, assay, impurities, visible and sub-visible particles, microbial contamination). Shelf life and

storage conditions after first opening and/or after reconstitution and/or dilution should be defined. These studies are not required if the preparation is to be used immediately after opening or reconstitution and if it can be justified that no negative influence on the quality of the preparation through instabilities is to be expected.

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

Information for phase I clinical trials

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

Additional information for phase II and phase III clinical trials

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

For radiopharmaceuticals, the time of calibration should be specified. The general stability guidelines are not fully applicable for ready-for-use radiopharmaceuticals, radio-nuclide generators and radioactive precursors.

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 Kingdom of Saudi Arabia (KSA) or in one of the ICH-regions (and are sourced from these countries), it will be sufficient to provide the name of the MA-holder and the MA-number as proof for the existence of a MA, incl. copy of the SmPC/Summary of

Product Characteristics or its equivalent e.g. Prescribing information. For repackaged/modified authorised products, see following chapter.

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

For IPs sourced from outside of the Kingdom of Saudi Arabia (KSA) or ICH regions, a full documentation, according to the requirements stated in chapter 2 of this guideline, should be submitted.

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

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

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

4.2.1.P Modified test/comparator product

4.2.1.P.1 Description and composition

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

4.2.1.P.2 Pharmaceutical development

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

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

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

4.2.1.P.3 Manufacture

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

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

When re-packaging and or re-labelling is carried out at a hospital, health center or clinic where the investigational product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, 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 new drug 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 United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food- chemical regulations (e.g. FCC) can be made. For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice. For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided. Specification for capsule shells should be provided.

4.2.P.4.2 Analytical procedures

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

4.2.1.P.4.3 Validation of analytical procedures

Not applicable.

4.2.1.P.4.4 Justification of specifications

Not applicable.

4.2.1.P.4.5 Excipients of animal or human origin

Cf. Appendix 7.2.1. A.2.

4.2.1.P.5 Control of the modified authorised product

4.2.1.P.5.1 Specifications

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

4.2.1.P.5.2 Analytical procedures

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

4.2.1.P.5.3 Validation of analytical procedures

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the results of validation of the analytical methods should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

4.2.1.P.5.4 Batch analyses

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

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

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

4.2.1.P.5.5 Characterisation of impurities

In those cases, where the authorised product has undergone significant modification by the sponsor, e.g. has been processed with an excipient hitherto not present in the formulation with a likely impact on product stability, and the original product is not known to be stable under normal conditions, special emphasis should be given to demonstrating that the impurity profile has not changed compared to the original product. For stable authorised products, where a small degree of modification has been undertaken by the sponsor, e.g. where an intact tablet is encapsulated using the ingredients already present in the tablet, justification for not quantifying impurities will suffice This is not required for authorised products which are only re- packaged.

4.2.1.P.5.6 Justification of specification(s)

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

4.2.1.P.7 Container closure system

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

4.2.1.P.8 Stability

The applicant or sponsor of the clinical trial has to ensure that the modified test/comparator product is stable for at least the anticipated duration of the clinical trial in which it will be used. In the case of any modification with a likely significant impact on product stability, a minimum of stability data on the modified authorised product should be available, depending on the length of the planned clinical trial, prior to the start of the clinical trial in order to allow an assessment of the impact of the modifications on product safety and stability. The available

stability data should be presented in a tabulated form. An evaluation of the available data and justification of the proposed shelf-life to be assigned to the IP in the clinical trial should be provided. Any degree of extrapolation may not exceed the shelf-life originally assigned to the specific batch of authorised product by its MAH.

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

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

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

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

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

5.S.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 "SFDA Drug Master File (DMF): Guidance for Submission should be followed, even though no specific reference to clinical trials application is included.

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

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

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

5.2.1.S.1 General information

5.2.1.S.1.1 Nomenclature

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

5.2.1.S.1.2 Structure

The structural formula should be presented.

5.2.1.S.1.3 General Properties

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

5.2.1.S.2 Manufacture

5.2.1.S.2.1 Manufacturer(s)

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

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

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

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

5.2.1.S.3 Characterisation

5.2.1.S.3.2 Impurities

For substances which comply with a monograph of the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been discussed.

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

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

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

5.2.1.S.4 Control of the drug substance

5.2.1.S.4.1 Specifications

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

For substances which comply with a monograph of the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia, no further details are required, provided its suitability to adequately control the quality of the active substance from the specific source has been demonstrated. The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts.

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

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

5.2.1.S.4.2 Analytical procedures

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

5.2.1.S.4.3 Validation of analytical procedures

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

5.2.1.S.4.4 Batch analyses

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

5.2.1.S.4.5 Justification of specifications

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

5.2.1.S.5 Reference Standards or materials

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

5.2.1.S.6 Container closure system

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

5.2.1.S.7 Stability

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

5.2.1.P Investigational product under test

5.2.1.P.1 Description and composition

The complete qualitative and quantitative composition of the IP should be stated. For proprietary prefabricated components (e.g. capsule shells), flavours and excipient mixtures (e.g. film-coating mixtures), a qualitative composition is sufficient.

5.2.1.P.2 Pharmaceutical development

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

5.2.1. P.3Manufacture

5.2.1.P.3.1 Manufacture

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

When re-packaging and or re-labelling is carried out at a hospital, health center or clinic where the investigational product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, 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 United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the

British Pharmacopoeia. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

5.2.1.P.4 Control of excipients

5.2.1.P.4.1 Specifications

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

5.2.1.P.4.2 Analytical procedures

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

5.2.1.P.4.3 Validation of analytical procedures

Not applicable.

5.2.1.P.4.4 Justification of specifications

Not applicable.

5.2.1.P.4.5 Excipients of animal or human origin

Cf. Appendix 7.2.1.A.2.

5.2.1.P.4.6 Novel excipients

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

5.2.1.P.5 Control of the investigational product

5.2.1.P.5.1 Specifications

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

The omission of drug product specific tests should be justified.

5.2.1.P.5.2 Analytical procedures

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

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

5.2.1.P.5.3 Validation of analytical procedures

The suitability of the analytical methods used should be demonstrated. A tabulated summary of the validation results should be provided (e.g. results or values found for specificity, linearity, range, accuracy, precision, quantification and detection limit, as appropriate). It is not necessary to provide a full validation report.

5.2.1.P.5.4 Batch analyses

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

5.2.1.P.5.5 Characterisation of impurities

Additional impurities/degradants observed in the IP, 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 IP 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. parenteral, ophthalmic products, oral solutions), more details may be needed. For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

5.2.1.P.8 Stability

For bioequivalence studies, it should be confirmed that an ongoing stability program will be carried out with the relevant batch(es) and that, prior to the start of the clinical trial, at least studies under accelerated and long-term storage conditions will have been initiated. The results

from at least one month accelerated studies or the results of the initial phase of studies under long-term storage conditions should be summarised in a tabulated form. Supporting data from development studies should also be summarised in a tabular overview. An evaluation of the available data and justification of the proposed shelf-life and storage conditions to be assigned to the IP in the bio-equivalence study should be provided. Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study.

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

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

6.2.1.P Placebo product in clinical trials

6.2.1.P.1 Description and composition

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

6.2.1.P.2 Pharmaceutical development

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

6.2.1.P.3 Manufacture

6.2.1.P.3.1 Manufacturer(s)

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

provided. In case that multiple manufacturers contribute to the manufacture of the placebo, their respective responsibilities need to be clearly stated.

When re-packaging and or re-labelling is carried out at a hospital, health center or clinic where the investigational product is to be used for the trial exclusively at those institutions, and where an exemption from the need to hold a manufacturing authorisation, it is not necessary to provide the names and addresses of those institutions in this section. If relevant, it is sufficient to indicate that these activities will take place.

6.2.1.P.3.2 Batch formula

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

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

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

6.2.1.P.3.4 Control of critical steps and intermediates

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

6.2.1.P.3.5 Process validation and/or evaluation

Data are not required, except for non-standard sterilisation processes not described in the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia. In this case, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

6.2.1.P.4 Control of excipients

6.2.1.P.4.1 Specifications

References to the United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia should be indicated. For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations

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

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 IPD 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 product and the placebo.

6.2.1.P.5.2 Analytical procedures

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

6.2.1.P.6 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.7 Stability

The shelf-life and storage conditions of the placebo should be defined. The shelf life of the placebo product should preferably cover the anticipated duration of the clinical trial. Stability studies are only required in cases where there is reason to suspect that the placebo product will undergo changes in its physical characteristics or degradation, respectively, e.g. microbial purity of multi-dose containers, hardness or appearance. In all other cases, a short justification of the assigned shelf-life will suffice.

7. Appendices

7.2.1.A.1 Facilities and equipment

Not applicable.

7.2.1.A.2 Adventitious agents safety evaluation

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

TSE agents

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

Viral safety

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

Other adventitious agents

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

7.2.1.A.3 Novel excipients

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

7.2.1.A.4 Solvents for reconstitution and diluents

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

8. Auxiliary new drugs

Auxiliary new drugs are defined as medicinal products used for the needs of a clinical trial as described in the protocol, but not as investigational products.

The same requirements and principles that apply to investigational products shall also apply to auxiliary new drugs. The requirements depend on the type of the drug (authorized, unauthorized, modified, or non-modified).

9. Changes to the investigational product and auxiliary new drug with a need to request a substantial amendment to the IPD

In accordance with Good Manufacturing Practice, a Product Specification File should be maintained for each IP/auxiliary new drug at the respective site and be continually updated as the development of the product proceeds, ensuring appropriate traceability to the previous versions.

In compliance with the Clinical Trial Regulation (CTR), a change to IP/auxiliary new drug quality data is either:

- a substantial amendment
- a non-substantial amendment (changes outside the scope of substantial modifications and changes irrelevant to the supervision of the trial)

Substantial amendment means any change which is likely to have a substantial impact on the safety and rights of the subjects or on the reliability and robustness of the data generated in the clinical trial.

Assessment of an IPD should be focus on patient safety. Therefore, any amendment involving a potential new risk shall be considered a substantial amendment

This may be especially the case for changes in the impurities profile, microbial contamination, viral safety, TSE and in some particular cases to stability when toxic degradation products may be generated, it is mandatory to obtain SFDA approval before implementing any substantial amendments the SFDA shall be notified via the annual progress report. However, when submitting a modified IPD, the sponsor shall clearly identify which changes are substantial and which are not.

When any quality modification will become effective with the start of a new clinical trial (e.g. change of name of the IPD, new manufacturing process), the notification takes place with the application for the new trial. Submissions of substantial modifications are only necessary for changes to ongoing clinical trials (i.e. after time of approval).

In the following table, examples are given for changes in IPDs, containing chemically defined or herbal drug substances, and their classification. This list does not claim to be exhaustive. The sponsor should decide on a case by case basis how to classify the change. In case of doubt, the sponsor should consult the SFDA

Changes to IPD	**Substantial** amendments	**Non-substantial** amendments
Manufacturer(s) of drug substance	• Addition of or a change to a new manufacturer (outside the company or within the company but in a different country) • Deletion of manufacturing or testing site (for quality/safety reason, GMP non- compliance)	• Alternate sites of manufacture within one company with unchanged manufacturing process and specifications • Name or address change of drug substance manufacturer provided that the manufacturing site and all manufacturing operations must remain the same • Deletion of a manufacturing or testing site (no quality/safety reason) • Replacement or addition of a testing site provided that the same analytical methods are used, and method transfer has been demonstrated

Manufacturing process of drug substance	• Different route of synthesis • Widening of the process parameters or IPC acceptance criteria with impact on product quality and safety • Changes in the physicochemical properties with influence on the quality of the IPD (e.g., particle size distribution, polymorphism in case of solid dosage forms etc.) • Change in the manufacturing process of an herbal substance or herbal preparation	• Modifications of the process parameters and widening of in-process acceptance criteria such that there is no impact to product quality (same process and synthetic route, albeit with possible slight modifications in solvents, reagents, catalysts, temperature, pressure, reaction time, or stoichiometry that do not impact the physicochemical properties or the impurity profile of the active substance) • Scale-up not impacting the physicochemical properties or the impurity profile • Changes in the physiochemical properties without influence on the quality of the IPD (e.g., particle size distribution for highly soluble drug, particle size distribution and/or polymorphism for a drug product

		that contains a spray dried dispersion)

Changes to IPD	**Substantial** amendments	**Non-substantial** amendments
		• Addition or tightening of IPC if not due to safety reasons • Addition of a reprocessing not described in the IPD (e.g., repetition of a purification step)
Specification of drug substance	• Widening of acceptance criteria • Deletion of specification parameter • Addition of specification parameter(s) for safety/quality reasons, e.g. addition of mutagenic impurity control	• Tightening of acceptance criteria (no safety reason) • Addition of specification parameter(s) with no safety reason • Addition, deletion or replacement of a specification parameter due to compendial change
Test methods of drug substance/ drug product	• New or different test method (e.g. NIR instead of HPLC) or method changes requiring new validation providing results that are not better or equivalent to the approved method, and/or impact the control strategy or specification	• Improvement of the same analytical method (e.g., greater sensitivity, precision, accuracy) provided • the acceptance criteria are similar or tighter • the improved method is suitable for use or validated according to the stage of development, and lead to comparable or better validation results • Update of the test procedure to comply with revised

		United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia monograph
Reference standard		• Introduction of new RS, provided equivalence has been established to the previous RS
Retest period of drug substance	• Reduction of retest period and/or restriction of the storage conditions due to safety and/or quality concern • Extension of retest period not based on the currently approved stability protocol or without prior commitment	• Extension of retest period based on the currently approved stability protocol or scheme • Reduction of retest period and/or change to more restrictive storage conditions provided that the change

Changes to IPD	**Substantial** amendments	**Non-substantial** amendments
	• Extension of stability protocol duration through additional timepoints to extend retest period	should not be the result of unexpected events arising during manufacture or because of stability concerns • Additional intermediate stability timepoint (e.g., additional pull point at 42 months) without changing the conditions for the extrapolation, leading to corresponding interim retest period extension
Change to the formulation of new drug	• Change in the qualitative or quantitative composition in one or more excipients that may have a significant impact on the quality or safety of the IPD (including exchange of excipients to excipients with same functional characteristics, e.g., disintegrate) • Change and/or addition of drug product strength	• Qualitatively identical but quantitatively different composition of non-functional tablet coating if there is no impact on blinding • Different shape of an IR-tablet, e.g. round to capsule shaped, with no clinical impact (e.g. dissolution profile of the new shape is comparable to the old one) and if there is no impact on blinding • Change of imprint/embossing/other markings provided it has no impact on blinding
Manufacturer(s) of the investigational product	• Addition or replacement of manufacturing, packaging, or testing site • Deletion of manufacturing,	• Deletion of manufacturing, packaging, or testing site (no safety reason) • Name changes of the manufacturer

	packaging, or testing site (for safety reason, GMP non-compliance) • Addition or replacement of batch release certification site (QP certification)	• Addition or replacement of an importation site that is not a QP certification site, with a valid GMP status
Manufacturing process of the investigational product	• Significant changes to the manufacturing process (e.g., dry compacting vs. wet granulation,	• Modifications of the process parameters (same process) where no effect on product quality is expected.

Changes to IPD	**Substantial** amendments	**Non-substantial** amendments
	conventional granulation vs. fluid-bed- granulation) and critical process controls (e.g. bioburden limit) • Scale-up for non-standard processes or large scale-ups such as that the multiplicatio factor for the scale-up exceeds 10 for standard manufacturing processes	• Scale-up (such as that the multiplication factor for the scale-up does not exceed 10) for standard manufacturing processes
Specification of excipients where thes may affect product performance	• Changes in the particle size distribution with influence o in-vitro dissolution	
Test methods of non-pharmacopoeial excipients	• New or different test method (e.g. NIR instead of HPLC)	• Minor changes of the analytical method already covered by the ID • Update of the test procedure to comply with United States Pharmacopoeia, European Pharmacopoeia, International Pharmacopoeia or the British Pharmacopoeia

Specification (release or shelf-life) of the new drug	• Widening of acceptance criteria with clinical relevance, e.g. change in the hardness with influence on the disintegration time and/o the in vitro- dissolution, or widening of acceptance criteria for impurities • Deletion of specification parameter(s) • Addition of specification parameter(s) with clinical relevance or for quality/safet reasons (e.g., to control polymorphs in the drug product that have the potential to change during manufacture or on stability, t monitor unqualified impurities, or to control mutagenic impurities)	• Tightening of acceptance criteria (no safety reason) • Addition of specification parameter(s) (no safety reason, control of mutagenic impurities excluded)

Changes to IPD	**Substantial** amendments	**Non-substantial** amendments
Container closure system	• New container closure system is introduced (e.g., less protective material, different container/material for liquid product)	
Medical devices	• Addition of, changes to, or replacement of, a medical device in the IPD that potentially impacts the quality, safety and/or efficacy.	• Changes to, or replacement of, a medical device in the IPD which is not considered to impact the quality, safety and/or efficacy.
Stability of the investigational product	• Reduction of shelf-life and/or restriction of the storage conditions due to safety and/or quality concern • Any extension of the shelf life not based on the currently approved stability protocol or without prior commitment • Extension of stability protocol duration through additional timepoints to extend shelf-life	• Extension of shelf-life based on the currently approved stability protocol or scheme • Additional intermediate stability timepoint (e.g., additional pull point at 42 months) without changing the conditions for the extrapolation, leading to corresponding interim shelf life extension