DECISION

No. 15/23.05.2008

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

The Scientific Council of the National Medicines Agency,
set up based on Minister of Public Health Order No. 1027/22.05.2008, as amended, reunited on summons of the National Medicines Agency President in the ordinary meeting of 23.05.2008, in accord with Article 10 of Government Ordinance no. 125/1998 related to the set up, organisation and functioning of the National Medicines Agency, approved as amended through Law No. 594/2002, as further amended, agrees on the following

DECISION

Single article - The Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials is approved, according to the Annexes, which are integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Medicines Agency

Acad. Prof. Dr. Victor Voicu

ANNEX

GUIDELINE
on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials

CHAPTER I

I.1 General Principles

Article 1. – This Guideline is a translation into Romanian and an adaptation of Guideline CHMP/QWP/185401/2004/final on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials.

I.2 Objectives

Article 2. – This Guideline is to be seen in connection with Minister of Public Health Order No. 904/25.07.2006 on the approximation of Norms relating to the implementation of the Good Clinical Practices in the conduct of clinical trials on medicinal products for human use, transposing Directive 2001/20/CE, on the harmonisation of legislation, regulations and administrative measures taken by member states, on the implementation of the Good Clinical Practices in the conduct of clinical trials (GCPSC) on medicinal products for human use, which came into force on July 28, 2006, and the respective Scientific Council Decision (SCD) No. 49/15.12.2006 on approval of the Guideline 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 Romania; the latter describes the structure of the chemical-pharmaceutical data to be submitted in the Investigational Medicinal Product Dossier (IMPD); however, this provides no guidance on the required detail of information.

Article 3. - 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 (EC).

Article 4. – (1) It should be clearly differentiated between the requirements for a dossier for a clinical trial and a marketing authorisation dossier.

(2) 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.

(3) As a consequence, it will not be possible to define very detailed requirements applicable to all sorts of different medicinal products.

(4) However, guidance on standard information which should normally be presented in the quality part of an IMPD is provided in this guideline.

I.3 Scope

Article 5. – (1) 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.

(2) The Guideline 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 bioequivalence studies.

(3) The section on authorised non-modified comparator products includes details on the extent of testing necessary to confirm their quality as required by Article 50 (1) of Minister of Public health Order No. 904/2006.

Article 6. – (1) 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 medicinal product have to be taken into account compared to phase I clinical studies.

(2) Based on the diversity of medicinal 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 not exhaustive.

(3) IMPs based on innovative and/or complex technologies may need more additional data to be submitted.

(4) 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 SCD No. 49/15.12.2006 “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.

I.4 General Points Concerning all IMPs

Article 7. - IMPs should be produced in accordance with the principles and the detailed guidelines of Good Manufacturing Practices for Medicinal Products for human use (The Rules Governing Medicinal Products in The European Community, Volume IV).

I.5 Submission of data

Article 8. – (1) In addition to the numeration given in the SCD No. 49/15.12.2006, the headings of the Guideline are preceded by an additional Roman number to facilitate the Guideline's use.

(2) However, the numbering in the IMPD should follow the numbering given in the SCD No. 49/15.12.2006.

(3) The above-mentioned preceding number should be omitted in the documentation.

I.6 General Considerations

Article 9. - (1) For IMPs to be used in clinical trials as described in chapters II to VI, 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.

(2) 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.

Article 10. - For generic bioequivalence studies as described in chapter V 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.

Article 11. - For impurities in IMPs, a justification that the medicinal product is safe for its intended use, considering the anticipated exposure of volunteers and patients, respectively, will be required.

Article 12. – (1) When compiling the documentation, the difference between "analytical procedure" and "analytical method" should be kept in mind.

(2) The term "analytical procedure" is defined in ICH Q 2 (A) and refers to the way of performing the analysis.

(3) The term "analytical method" refers to the principles of the method used.

CHAPTER II
Information on the chemical and pharmaceutical properties of investigational medicinal products

II.2.1.S Drug substance

Article 13. – (1) Reference to an Active Substance Master File or a "Certificate of Suitability of the European Directorate for the Quality of Medicines" is acceptable.

(2) 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.

Article 14. - For reference to pharmacopoeial monographs, see section 1.6 General Considerations.

II.2.1.S.1 General Information

II.2.1.S.1.1 Nomenclature

Article 15. – (1) 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.

(2) 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.

Article 16. - For radio-nuclides, the isotope type should be stated (IUPAC-nomenclature).

Article 17. – (1) In the case of radionuclide generators, both parent radionuclide and daughter radionuclide are considered as drug substances.

(2) 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.

(3) For organic-chemical precursors, the same information should be provided as for drug substances.

Article 18. - 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.

Article 19. – 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.

II.2.1.S.1.2 Structure

Article 20. – (1) The data available at the respective stage of clinical development should be presented.

(2) They should include the structural formula, molecular weight, chirality/stereochemistry as far as elucidated.

Article 21. – (1) 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.

(2) - For kits for radiopharmaceutical preparations, the ligand's structural formula before and, if known, after the radio-labelling should be given.

Article 22. – (1) 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.

(2) Information about excipients in the final herbal preparations should also be provided.

II.2.1.S.1.3 General Properties

Article 23. - 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 solubility, pKa, polymorphism, isomerism, log P, permeability etc..

Article 24 - For radio-nuclides, the nuclear and radiophysical properties should be stated.

II.2.1.S.2 Manufacture

II.2.1.S.2.1 Manufacturer(s)

Article 25. - 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.

Article 26. – (1) In 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.

(2) For radiopharmaceuticals, the manufacturer of the radiopharmaceutical precursors and of non-radioactive precursors should be stated.

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

Article 27. – (1) 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.

(2) Any relevant process controls should be indicated.

(3) Where critical steps in the synthesis have been identified, a more detailed description may be appropriate.

(4) The stereochemical properties of starting materials should be discussed, where applicable.

(5) 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.

Article 28. – (1) For radio-nuclides, the nuclear reactions should be described, including possible undesired nuclear reactions.

(2) The conditions for irradiation should be given.

(3) The cleaning and segregation processes for the radiopharmaceutical preparation and the organic-chemical precursors should be stated.

Article 29. – (1) 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.

(2) The in-process controls carried out should be documented.

(3) The main production steps should be indicated.

Article 30 - The production scale or range of batch sizes to be used in the clinical trial should be stated.

II.2.1.S.2.3 Control of materials

Article 31. - 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..

II.2.1.S.2.4 Control of Critical Steps and Intermediates

Article 32. - In case of critical steps in the synthesis, tests and acceptance criteria for their control should be briefly summarised.

II.2.1.S.2.5 Process Validation and/or Evaluation

Article 33. - Not applicable for drug substances to be used in clinical trials.

II.2.1.S.2.6 Manufacturing Process Development

Article 34. – (1) 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.

(2) In this case, a flow chart of the manufacturing process used for the drug substance used in the non-clinical studies should be presented.

II.2.1.S.3 Characterisation

II.2.1.S.3.1 Elucidation of Structure and other Characteristics

Article 35. - 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.

Article 36. - In this case, a flow chart of the manufacturing process used for the drug substance used in the non-clinical studies should be presented.

Article 37. – (1) For herbal substances, information should be given on the botanical, macroscopic and microscopic and phytochemical characterisation.

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

(3) For herbal preparations, details should be provided on the physical and phytochemical characterisation.

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

II.2.1.S.3.2 Impurities

Article 38. - 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.

Article 39. - 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.

Article 40. – (1) 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.

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

Article 41. – (1) For herbal substances or herbal preparations, data on potential contamination by micro-organisms, products of micro-organisms, pesticides, toxic metals, radioactive contamination, fumigants, etc. should be stated.

(2) The general requirements of the Ph. Eur. should be fulfilled.

II.2.1.S.4 Control of the drug substances

II.2.1.S.4.1 Specifications

Article 42. – (1) The specifications, the tests used as well as their acceptance criteria should be specified for the batch(es) of medicinal product(s) used in the clinical trial.

(2) Tests for identity and assay are mandatory.

(3) Upper limits, taking safety considerations into account, should be set for the impurities.

(4) These may need to be reviewed and adjusted during further development.

Article 43. - The microbiological quality for drug substances used in aseptically manufactured products should be specified.

Article 44. – (1) For substances which comply with the monographs 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.

(2) The specification should, however, include acceptance criteria for any relevant residual solvent or catalyst.

Article 45. - 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

Article 46. - 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.

II.2.1.S.4.2 Analytical procedures

Article 47. - (1) 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.).

(2) It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter I.6. General Considerations)

Article 48. - For radiopharmaceutical substances, the method used for the measurement of radioactivity should be described.

Article 49. - 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.

II.2.1.S.4.3 Validation of analytical procedures

Article 50. – (1) For phase I clinical trials, the suitability of the analytical methods used should be confirmed.

(2) 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

Article 51. – (1) The suitability of the analytical methods used should be demonstrated.

(2) 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).

(3) It is not necessary to provide a full validation report.

Article 52. - 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.

II.2.1.S.4.4 Batch Analysis

Article 53. – (1) 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.

(2) 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.

Article 54. - The batch number, batch size, manufacturing site, manufacturing date, control methods, acceptance criteria and the test results should be listed.

Article 55. – The manufacturing process used for each batch should be assigned as stated under 2.2.1.S.2.2.

II.2.1.S.4.5 Justification of specification

Article 56. – (1) For substances for which reference to the pharmacopoeias listed under II.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 medicinal product should be provided based on safety and toxicity data, as well as the methods used for the control of impurities.

(2) The solvents and catalysts used in the synthesis should be taken into consideration.

II.2.1.S.5 Reference standards or materials

Article 57. - The parameters characterising the batch of drug substance established as reference standard should be presented, where applicable.

Article 58. - For radiopharmaceuticals, data on the standards used for calibration and the non-radioactive (cold) standards should be provided.

Article 59. – (1) For herbal preparations, the parameters characterising the primary reference standards should be given.

(2) 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.

II.2.1.S.6 Container closure system

Article 60. - The immediate packaging material used for the drug substance should be stated.

II.2.1.S.7 Stability

Article 61. – (1) The stability data available at the respective stage of development should be summarised in tables.

(2) 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.

(3) Potential degradation pathways should be described.

(4) Alternatively, for active substances covered by a pharmacopoeial monograph, confirmation that the active substance will meet specifications at time of use will be acceptable.

Article 62. - For herbal preparations, results of stress testing may be omitted, where justified.

II.2.1.P Investigational medicinal product under test

II.2.1.P.1 Description and Composition of the Investigational Medicinal Product:

Article 63. - The qualitative and quantitative composition of the IMP should be stated, including a short statement or a tabulation of the dosage form and the function of each excipient.

Article 64. - In addition, the radioactivity per unit should be specified for radiopharmaceuticals.

II.2.1.P.2 Pharmaceutical development

Article 65. - A short description of formulation development, including justification of any new pharmaceutical form or excipient, should be provided.

Article 66. - For early development, there may be no or only limited information to include in this section.

Article 67. – (1) Where applicable, the compatibility with solvents used for reconstitution, diluents and admixtures should be demonstrated.

(2) 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.

Article 68. – (1) 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).

(2) For radionuclide generators, the suitability of the elution medium should be proven.

(3) 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

Article 69. – (1) 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.

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

II.2.1.P.2.3 Manufacturing process development

Article 70. – (1) Changes in the current manufacturing process compared to the one used in phase I and phase II clinical trials, respectively, are to be explained.

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

II.2.1.P.3 Manufacture

II.2.1.P.3.1 Manufacturer(s)

Article 71. – (1) The name(s), address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided.

(2) In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

Article 72. – (1) 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 Minister of Public Health Order No. 904/25.07.2006, it is not necessary to provide the names and addresses of those institutions in this section.

(2) If relevant, it is sufficient to indicate that these activities will take place.

II.2.1.P.3.2 Batch formula

Article 73. – (1) The batch formula for the batch to be used for the clinical trial should be presented.

(2) Where relevant, an appropriate range of batch sizes may be given.

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

Article 74. – (1) A flow chart of the successive steps, indicating the components used for each step and including any relevant in-process controls, should be provided.

(2) In addition, a brief narrative description of the manufacturing process should be included.

Article 75. - 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).

II.2.1.P.3.4 Controls of Critical Steps and Intermediates

Article 76. - Information is not required for phase I and II clinical trials, with the exception of

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

Additional information for phase III clinical trials

Article 77. - If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.

Article 78. - Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

II.2.1.P.3.5 Process validation and/or evaluation

Article 79. – (1) 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.

(2) In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

II.2.1.P.4 Control of excipients

II.2.1.P.4.1 Specifications

Article 80. – (1) References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.

(2) For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food-chemical regulations (e.g. FCC) can be made.

(3) For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice.

(4) For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.

II.2.1.P.4.2 Analytical procedures

Article 81. - In cases where reference to a pharmacopoeial monograph listed under II.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

II.2.1.P.4.3 Validation of the analytical procedures

Article 82. – Not applicable.

II.2.1.P.4.4 Justification of specifications

Article 83. – Not applicable.

II.2.1.P.4.5 Excipients of human or animal origin

Article 84. – Cf. section VII.2.1.A.2.

II.2.1.P.4.6 novel excipients

Article 85. – (1) For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety.

(2) 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.

II.2.1.P.5 Control of the investigational medicinal product

II.2.1.P.5.1 Specifications

Article 86. - The chosen release and shelf life specifications should be submitted, including test methods and acceptance criteria.

Article 87. – (1) Upper limits may be set for each individual degradation product and the sum of degradation products.

(2) 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.

(3) The specifications and acceptance criteria should be reviewed and adjusted during further development.

Article 88. – (1) For radiopharmaceuticals, it should be specified which tests are carried out prior to batch release and which tests are carried out retrospectively.

(2) For kits for radiopharmaceutical preparations, appropriate tests after radioactive radio-labelling should be stated.

Article 89. - 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

Article 90. - 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.

II.2.1.P.5.2 Analytical procedures

Article 91. - The analytical methods should be described for all tests included in the specification (e.g. dissolution test method).

Article 92. - For complex or innovative pharmaceutical forms, a higher level of detail may be required.

II.2.1.P.5.3 Validation of analytical procedures

Article 93. – (1) For phase I clinical trials, the suitability of the analytical methods used should be confirmed.

(2) 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

Article 94. – (1) The suitability of the analytical methods used should be demonstrated.

(2) 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).

(3) It is not necessary to provide a full validation report.

II.2.1.P.5.4 Batch Analysis

Article 95. - Results or certificates of analysis for batches representative for the IMP to be used in the clinical study should be provided.

Article 96. - 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).

II.2.1.P.5.5 Characterisation of impurities

Article 97. - Additional impurities/degradants observed in the IMP, but not covered by section 2.2.1.S.3.2, should be stated.

II.2.1.P.5.6 Justification of specification(s)

Article 98. – (1) 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 medicinal product.

(2) Toxicological justification should be given, where appropriate.

Additional information for phase II and III clinical trials

Article 99. - The choice of specifications and acceptance criteria for parameters which may affect efficacy or safety should be briefly justified.

II.2.1.P.6 reference standards or materials

Article 100. – The parameters for characterisation of the reference standard should be submitted, where applicable.

Article 101. - Section II.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable.

II.2.1.P.7 Container closure system

Article 102. – (1) 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.

(2) Where appropriate, reference should be made to the relevant pharmacopoeial monograph.

(3) If the medicinal product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided.

(4) 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.

(5) For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

II.2.1.P.8 Stability

Article 103. – (1) 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.

(2) Extrapolation may be used, provided that stability studies are conducted in parallel to the clinical studies and throughout its entire duration.

(3) 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.

(4) A stability commitment should be provided.

(5) Furthermore, bracketing and matrixing designs of appropriate IMPs may be acceptable, where justified.

(6) The batches of drug product must meet specification requirements throughout the period of use.

(7) If issues arise, then the Competent Authorities should be informed of the situation, including any corrective action proposed.

Article 104. – (1) For preparations intended for multiple applications after reconstitution, dilution or mixing, in-use stability data should be presented.

(2) 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.

Article 105. - 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

Article 106. – (1) 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.

(2) Where available, the results from these studies should be summarised in a tabulated form.

(3) Supportive data from development studies should be summarised in a tabular overview.

(4) 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

Article 107. – (1) The available stability data should be presented in a tabulated form.

(2) 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.

(3) Data should include results from studies under accelerated and long-term storage conditions.

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

Article 108. – (1) For test and comparator medicinal 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.

(2) For repackaged comparator products, see following chapter.

Article 109. – (1) For medicinal 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.

(2) The relevant analyses, tests or checks necessary to confirm quality as required by Article 50 (1) c) of Minister of Public health Order No. 904/2006 shall therefore be based on proof of existence of the equivalent of a marketing authorisation, combined with confirmation of identity.

Article 110. – (1) 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.

(2) For authorised medicinal products, it will be sufficient to state the respective expiry date assigned by the manufacturer.

Article 111. - 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 II of this guideline, should be submitted.

CHAPTER IV
Information on the chemical and pharmaceutical quality of modified authorised comparator products in clinical trials

Article 112. - 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.

Article 113. - As the marketing authorisation holder (MAH) of a comparator product is only responsible for the unchanged product in its designated and authorised packaging, there is a need to ensure that the quality of the medicinal 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.

IV.2.1.P Modified comparator product

IV.2.1.P.1 Description and composition

Article 114. – (1) In the case of any modification of the authorised medicinal product other than repackaging, the complete quantitative composition of the preparation should be specified.

(2) All additional substances/materials added to the authorised medicinal product should be listed with reference to pharmacopoeial or in-house monographs.

(3) 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.

IV.2.1.P.2 Pharmaceutical Development

Article 115. – (1) The modifications carried out on the authorised comparator product should be described and their influence on the quality of the medicinal product discussed.

(2) 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.

(3) It should be demonstrated that these parameters remain comparable to those of the unmodified medicinal product.

Article 116. – (1) 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.

(2) In those cases where comparability cannot be established in vitro, additional clinical data to support equivalence may be necessary.

IV.2.1.P.3 Manufacture

IV.2.1.P.3.1 Manufacturer(s) related to the Modification

Article 117. – (1) 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 product should be provided.

(2) In case that multiple manufacturers contribute to the manufacture of the IMP, their respective responsibilities need to be clearly stated.

Article 118. – (1) 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 Minister of Public Health Order No. 903/25.07.2006, Art 24 (4), it is not necessary to provide the names and addresses of those institutions in this section.

(2) If relevant, it is sufficient to indicate that these activities will take place.

IV.2.1.P.3.2 Batch Formula

Article 119. – (1) The batch formula for the batch intended to be used during the clinical trial should be presented.

(2) This does not apply to authorised medicinal products which are only re-packaged.

IV.2.1.P.3.3 Description of In-Process Manufacturing Process and Process Controls

Article 120. – (1) All steps of the modification of the authorised medicinal product should be described, including in-process controls that are carried out.

(2) For details, reference is made to section. II.2.1.P.3.3).

IV.2.1.P.4 Control of excipients

IV.2.1.P.4.1 Specifications

Article 121. – (1) References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.

(2) For excipients not described in any of the mentioned pharmacopoeias, reference to the relevant food chemical regulations (e.g. FCC) can be made.

(3) For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice.

(4) For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.

IV.2.1.P.4.2 Analytical procedures

Article 122. - In cases where reference to a pharmacopoeial monograph listed under IV.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

IV.2.1.P.4.3 Validation of analytical procedures

Article 123. – Not applicable.

IV.2.1.P.4.4 Justification of specifications

Article 124. – Not applicable.

IV.2.1P.4.5 Excipients of human or animal origin.

Article 125. – Cf. Appendix VII.2.1.A.2.

IV.2.1.P.5 Control of the modified comparator product

IV.2.1.P.5.1 Specifications

Article 126. – (1) The chosen release and shelf-life specifications of the modified comparator product should be submitted, including information on test methods and acceptance criteria.

(2) 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.

(3) 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.

(4) Depending on the degree of modification of the authorised medicinal product, additional quality criteria, e.g. determination of the drug substance(s) and impurities/degradants, may need to be specified and tested.

IV.2.1.P.5.2 Analytical procedures

Article 127. - For parameters relevant to the performance of the comparator product, e.g. dissolution, the methods should be described.

IV.2.1.P.5.3 Validation of analytical procedures

Article 128. – (1) The suitability of the analytical methods used should be demonstrated.

(2) 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).

(3) It is not necessary to provide a full validation report.

IV.2.1.P.5.4 Batch analysis

Article 129. - 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.

Article 130. – 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 SCD No. 49/15.12.2006 on the approval of the "Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of important amendments and the declaration of a closure of a clinical trial in Romania " in its current version).

IV.2.1.P.5.5 Characterisation of purities

Article 131. – (1) 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.

(2) For stable comparator products, where a small degree of modification has been undertaken by the sponsor, 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").

(3) This is not required for authorised medicinal products which are only re-packaged.

IV.2.1.P.5.6 Justification of specification(s)

Article 132. - A justification of specification(s) will only be required in cases where a significant modification of the authorised comparator product may affect the medicinal product's performance or safety.

IV.2.1.P.7 Container closure system

Article 133. – (1) The type of immediate packaging, material and package size(s) should be specified.

(2) If materials other than those authorised are used, a description and specifications should be provided.

(3) Where appropriate, reference should be made to the relevant pharmacopoeial monograph.

IV.2.1.P.8 Stability

Article 134. - 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.

Article 135. – (1) 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 medicinal product safety and stability.

(2) The available stability data should be presented in a tabulated form.

(3) 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.

(4) Any degree of extrapolation may not exceed the shelf-life originally assigned to the specific batch of authorised medicinal product by its MAH.

Article 136. - In the case of only minor modifications, a justification of the stability over the intended study period may be acceptable.

CHAPTER V

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

Article 137. – (1) This section of the guideline is only relevant for the test product.

(2) Information on the comparator/innovator medicinal product to be provided in the IMPD should meet the requirements as outlined in sections 3 and 4, respectively.

V.2.1.S Drug substance

Article 138. – (1) Reference to an Active Substance Master File or a Certificate of Suitability of the European Directorate for the Quality of Medicinal Products is acceptable.

(2) 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.

Article 139. - For reference to pharmacopoeial monographs, see section I.6. General Considerations.

V.2.1.S.1 General Information

V.2.1.S.1.1 Nomenclature

Article 140. - 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.

V.2.1.S.1.2 Structure

Article 141. - The structural formula of the medicinal product should be presented.

V.2.1.S.1.3 General Properties

Article 142. - The main physicochemical and other relevant properties of the drug substance should be indicated.

V.2.1.S.2 Manufacture

V.2. 1.S.2.1 Manufacturer(s)

Article 143. - The name(s) and address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing of the medicinal product should be provided.

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

Article 144. - 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.

Article 145. – (1) 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 in the manufacturing process should be provided.

(2) The stereochemical properties of starting materials should be discussed, where applicable.

V.2.1.S.3 Characterisation

V.2.1.S.3.2 Impurities

Article 146. - 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.

Article 147. - 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.

V.2.1.S.4 Control of the drug substance

V.2.1.S.4.1 Specifications

Article 148. - The microbiological quality of drug substances used in aseptically manufactured products should be specified.

Article 149. – (1) 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.

(2) The specification should, however, include acceptance criteria for any relevant residual solvents and catalysts.

Article 150. - 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.

V.2.1.S.4.2 Analytical procedures

Article 151. – (1) For substances for which reference to a pharmacopoeial monograph listed under V.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.

(2) It is not necessary to provide a detailed description of the analytical procedures (see definition of analytical methods vs. analytical procedures in chapter I.6. General Considerations).

V.2.1.S.4.3 Validation of analytical procedures

Article 152. – (1) For substances for which reference to a pharmacopoeial monograph listed under V.2.1.S.4.1 of this chapter cannot be made, the suitability of the analytical methods used should be demonstrated.

(2) 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.)

(3) It is not necessary to provide a full validation report.

V.2.1.S.4.4 Batch analysis

Article 153. – (1) Certificates of analyses or batch analysis data for the batch(es) intended for use in the planned bioequivalence study or, in their absence, for representative batches, should be supplied.

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

V.2.1.S.4.5 Justification of specifications

Article 154. – (1) For substances for which reference to a pharmacopoeial monograph listed under V.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.

(2) Just justification should be based on safety and toxicity information, as well as on the methods employed for the control of impurities.

(3) The solvents and catalysts used in the synthesis should be taken into consideration.

V.2.1.S.5 Reference standards or materials

Article 155. - For substances for which reference to a pharmacopoeial monograph listed under V.2.1.S.4.1 cannot be made, the parameters characterising the batch of drug substance established as reference standards should be presented.

V.2.1.S.6 Container closure system

Article 156. - The immediate packaging material used for the drug substance should be stated.

V.2.1.S.7 Stability

Article 157. – (1) The available stability data should be provided in a tabulated form.

(2) Alternatively, confirmation that the active substance will meet specifications at time of use will be acceptable.

V.2.1.P Investigational medicinal product under test

V.2.1.P.1 Description and composition

Article 158. - The qualitative and quantitative composition of the IMP should be stated.

V.2.1.P.2 Pharmaceutical development

Article 159. – A short description of the pharmaceutical form should be provided.

V.2.1.P.3 Manufacture

V.2.1.P.3.1 Manufacturer(s)

Article 160. – (1) The name(s), address(es) and responsibilities of all manufacturer(s), including contractors, and each proposed production site involved in manufacture and testing should be provided.

(2) 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 Article 24 (4) of Minister of Public Health Order No. 903/25.07.2006 applies, it is not necessary to provide the names and addresses of those institutions in this section.

(3) If relevant, it is sufficient to indicate that these activities will take place.

V.2.1.P.3.2 Batch formula

Article 162. – (1) The batch formula for the batch to be used in the planned bio-equivalence study should be presented in the clinical trial.

(2) Where relevant, an appropriate range of batch sizes may be given.

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

Article 163. – (1) A flow chart of the successive steps, including the components used for each step and including any relevant in process controls, should be provided.

(2) In addition, a brief narrative description of the manufacturing process should be included.

V.2.1.P.3.4 Control of Critical Steps and Intermediates

Article 164. - If critical manufacturing steps have been identified; their control as well as possible intermediates should be documented.

Article 165. - Should intermediates be stored, assurance should be provided that duration and conditions of storage are appropriately controlled.

V.2.1.P.3.5 Process validation and/or evaluation

Article 166. – (1) Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., USP or JP and non-standard manufacturing processes.

(2) 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).

V.2.1.P.4 Control of excipients

V.2.1.P.4.1 Specifications

Article 167. – (1) References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.

(2) For excipients not described in one of the aforementioned pharmacopoeias, reference to the relevant food – chemical regulations (e.g. FCC) can be made.

(3) For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice.

(4) For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.

V.2.1.P.4.2 Analytical procedures

Article 168. - In cases where reference to a pharmacopoeial monograph listed under V.2.1.P.4.1 cannot be made, the analytical methods used should be indicated.

V.2.1.P.4.3 Validation of analytical procedures

Article 169. – Not applicable.

V.2.1.P.4.4 Justification of specifications

Article 170. – Not applicable.

V.2.1.P.4.5 Excipients of human or animal origin

Article 171. – Cf. Appendix VII.2.1.A.2.

V.2.1.P.4.6 Novel Excipients

Article 172. – (1) For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety.

(2) 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 VII.2.1.A.3), details are to be included on e.g. their manufacturing process, characterisation and stability.

V.2.1.P.5 Control of the investigational medicinal product

V.2.1.P.5.1 Specifications

Article 173. - The chosen release and shelf life specifications should be submitted, including test methods and acceptance criteria.

V.2.1.P.5.2 Analytical procedures

Article 174. - The analytical methods should be described for all tests included in the specification (e.g. dissolution test method).

Article 175. - For complex or innovative pharmaceutical forms, a higher level of detail may be required.

V.2.1.P.5.3 Validation of Analytical Procedures

Article 176. – (1) The suitability of the analytical methods used should be demonstrated..

(2) 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).

(3) It is not necessary to provide a full validation report.

V.2.1.P.5.4 Batch analysis

Article 177. - Certificates of analysis or batch analysis data for the batch(es)

intended to be used in the planned bioequivalence study or, in their absence, representative batches, should be provided.

Article 178. - 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 SCD No. 49/15.12.2006 on the approval of the "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 a trial in Romania" in its current version).

V.2.1.P.5.5 Characterisation of Impurities

Article 179. – Information on the impurities or the additional degradation products observed in the IMP and which have not been mentioned in section V.2.1.S.3.2. should be mentioned.

V.2.1.P.5.6 Justification of Specification(s)

Article 180. – (1) 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 medicinal product.

(2) Toxicological justification should be given, where appropriate.

V.2.1.P.6 Reference Standards or Materials

Article 181. - The parameters for characterisation of the reference standard should be submitted, if no compendial reference standard is available.

Article 182. - Section V.2.1.S.5 - Reference Standards or Materials - may be referred to, where applicable.

V.2.1.P.7 Container Closure System

Article 183. – (1) 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.

(2) Where appropriate, reference should be made to the relevant pharmacopoeial monographs.

(3) If the medicinal product is packed in a non-standard administration device, or if non-compendial materials are used, a description and specifications should be provided.

(4) For dosage forms that have a higher potential for interaction between filling and container closure system (e.g. parenterals, ophthalmic medicinal products, oral solutions), more details may be needed.

(5) For dosage forms where an interaction is unlikely, e.g. solid oral dosage forms, a justification for not providing any information may suffice.

V.2.1.P.8 Stability

Article 184. – (1) 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.

(2) 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.

(3) Supporting data from development studies should also be summarised in a tabular overview.

(4) 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.

(5) Extrapolation may be used, provided a commitment is included to perform an ongoing stability study in parallel to the bioequivalence study.

CHAPTER VI
Information on the chemical and pharmaceutical quality concerning placebo products in clinical trials

Article 185. - The quality documentation to be submitted for placebos is limited to the following sections of the product part.

VI.2.1.P Placebo product in clinical trials

VI.2.1.P.1 Description and composition

Article 186. – (1) The qualitative and quantitative composition of the placebo should be stated.

(2) A short statement or a tabulation of the dosage form and the function of each excipient should be included.

VI.2.1.P.2 Pharmaceutical Development

Article 187. - It should describe how possible differences of the placebo preparation in relation to the investigational medicinal product regarding taste, appearance and smell are masked, where applicable.

VI.2.1.P.3 Manufacture

VI.2.1.P.3.1 Manufacturer(s)

Article 188. – (1) 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.

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

Article 189. – (1) 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 Article 24 (4) of Minister of Public Health Order No. 903/25.07.2006 applies, it is not necessary to provide the names and addresses of those institutions in this section.

(2) If relevant, it is sufficient to indicate that these activities will take place.

VI.2.1.P.3.2 Batch Formula

Article 190. – (1) The batch formula for the batch to be used for the clinical trial should be presented.

(2) Where relevant, an appropriate range of batch sizes may be given.

VI.2.1.3.3 Description of Manufacturing Process and Process Controls

Article 191. – (1) A flow chart of the successive steps, indicating the components used for each step and including in-process controls should be provided.

(2) In addition, a brief narrative description of the manufacturing process should be included.

VI.2.1.P.3.4 Control of Critical Steps and Intermediates

Article 192. - Information is not required with the exception of manufacturing processes for sterile medicinal products.

VI.2.1.P.3.5 Process Validation and/or Evaluation

Article 193. – (1) Data are not required, except for non-standard sterilisation processes not described in the Ph. Eur., the pharmacopoeia of a member state, USP or JP.

(2) In these cases, the critical manufacturing steps, the validation of the manufacturing process as well as the applied in process controls should be described.

VI.2.1.P.4 Control of Excipients

VI.2.1.P.4.1 Specifications

Article 194. – (1) References to the Ph. Eur., the pharmacopoeia of an EU Member State, USP or JP should be indicated.

(2) For excipients not described in one of the mentioned pharmacopoeias, reference to the relevant food – chemical regulations (e.g. FCC) can be made.

(3) For excipient mixtures composed of pharmacopoeial substances, e.g. pre-fabricated dry mix for film-coating, a general specification of the mixture will suffice.

(4) For excipients not covered by any of the afore-mentioned standards, an in-house monograph should be provided.

VI.2.1.P.4.2 Analytical procedures

Article 195. - In cases where reference to a pharmacopoeial monograph listed under VII.1.4.1 cannot be made, the analytical methods used should be indicated.

VI.2.1.P.4.3 Validation of Analytical Procedures

Art.196. – Not applicable.

VI.2.1.P.4.4 Justification of Specification(s)

Article 197. – Not applicable.

VI.2.1.P.4.5 Excipients of human or animal origin

Article 198. – Cf. section **VII.2.1.A.2**

VI.2.1.P.4.6 Novel Excipients

Article 199. – (1) For novel excipients, details are to be given on their manufacturing process, characterisation and control in relevance to product safety.

(2) 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 VIII.3); details are to be included on e.g. their manufacturing process, characterisation and stability.

(3) If the same novel excipient is already described in the IMPD for the respective test medicinal product, cross-reference to the relevant section will suffice.

VI.2.1.P.5 Control of the investigational medicinal product

VI.2.1.P.5.1 Specifications

Article 200. – (1) The chosen release and shelf-life specifications should be submitted, including test methods and acceptance criteria.

(2) The specifications should at minimum include a test which enables to clearly differentiate between the respective investigational medicinal product and the placebo.

VII.1.5.2 Analytical procedures

Article 201. - The analytical methods should be described for all tests included in the specification.

VI.2.1.P.7 Container Closure System

Article 202. - 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.

VI.2.1.P.8 Stability

Article 203. – (1) 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.

(2) These stability studies are mandatory if there is a reason to suspect that the physical/degradation properties of the placebo product (e.g. bacterial purity of multidose containers, durity or aspect) shall undergo changes.

(3) In all the other cases, a justification of the established availability term is sufficient.

CHAPTER VII
Appendices

VII.2.1.A.1 Facilities and equipment

Article 204. – Not applicable.

VII.2.1.A.2 Adventitious Agents Safety Evaluation:

Article 205. – (1) All materials of human or animal origin used in the manufacturing process of both drug substance and drug product, as well as such materials coming into contact with drug substance or drug product during the manufacturing process, should be identified.

(2) 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

Article 206. – (1) Detailed information should be provided on the avoidance and control of transmissible spongiform encephalopathy agents (TSE).

(2) This information can include, for example, certification and control of the production process, as appropriate for the material, process and agent.

Article 207. - The provisions of the Minister of Public Health Order No. 1201/2006 on the approval of the "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products", transposing the EMEA/410/01 Guideline in its current version should be applied.

Viral safety

Article 208. – (1) Where applicable, information assessing the risk with respect to potential viral contamination should be provided in this section.

(2) The risk of introducing viruses into the medicinal product and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated.

Other adventitious agents

Article 209. - Detailed information regarding the other adventitious agents, such as bacteria, mycoplasma, and fungi should be provided in appropriate sections within the core dossier.

VII.2.1.A.3 Novel Excipients

Article 210. - For novel excipients, information as indicated in section.3.2.S of the CTD should be provided, consistent with the respective clinical phase..

VII.2.1.A.4 Solvents for Reconstitution and Diluents:

Article 211. - For solvents for reconstitution and diluents, the relevant information as indicated in section 3.2.P of the CTD should be provided as applicable.

CHAPTER VIII
Changes to the investigational medicinal product with a need to request a substantial amendment to the IMPD

Article 212. – (1) In accordance with the Good Manufacturing Practice provisions, 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 version.

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

Article 213. - The following examples of changes to IMP quality data shall be considered "important" only if they have an impact upon:

- 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.

Examples of such changes:

- 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

Article 214. – (1) In all cases, an amendment is only to be regarded as "substantial" where it is likely to fulfil one or several of the aforementioned criteria:

(2) The list is not exhaustive; a substantial amendment might occur in some other aspect of a clinical trial (cf. HCS No. 49/15.12.2006 on the approval of the "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 Romania" in its current version) .

Article 215. – (1) Assessment of an IMPD should be focussed on patient safety.

(2) Therefore, any amendment involving a potential new risk has to be considered a substantial amendment.

(3) 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.

Article 216. – (1) The amendments refer to the submitted IMPD.

(2) Should the changes be covered by the IMPD as submitted, a notification of a substantial amendment will not be necessary.

Article 217. – (1) 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.

(2) Notifications of substantial amendments are only necessary for changes in ongoing clinical trials.

Article 218. – (1) 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.

(2) This list does not claim to be exhaustive.

(3) The sponsor should decide on a case by case basis if an amendment is to be classified as substantial or not.