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GUIDELINE ON THE CHEMICAL AND PHARMACEUTICAL QUALITY REQUIREMENTS OF MEDICINAL PRODUCTS FOR HUMAN USE USED IN CLINICAL TRIALS KAD-KLVZ-27

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1. INTRODUCTION 1.1. Purpose and Legal Basis The purpose of this guideline is to determine the chemical and pharmaceutical quality requirements for medicinal products for human use to be used in clinical trials to be conducted in Turkey, taking national and international standards into consideration. This guideline is intended to clarify the difference and distinction between the requirements applicable to the investigational medicinal product dossier and those applicable to the marketing authorization dossier. When presenting information on investigational medicinal products, a risk-focused approach shall be adopted, taking into account the nature of the product, its stage of development, the clinical phase, the volunteer population, the nature and severity of the disease, and the type and duration of the clinical trial. This Guideline has been prepared taking into consideration the Regulation on Clinical Trials on Medicinal Products for Human Use published in the Official Gazette dated 27/05/2023 and numbered 32203, and, within the framework of alignment with European Union legislation, the Guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (EMA/CHMP/QWP/545525/2017). However, since different clinical trials and investigational medicinal products may be in question, it is not possible to define in detail requirements that would be applicable to all different situations. Nevertheless, this guideline includes explanations regarding the general information to be presented in the quality part of the investigational medicinal product dossier. The Agency and the relevant ethics committee may request additional information and documents where necessary. 1.2. Scope This guideline covers the dossier requirements concerning the chemical and pharmaceutical quality of investigational medicinal products containing chemical active substances, synthetic peptides, synthetic oligonucleotides, active substances in herbal medicinal products (herbal drug or herbal preparation) and chemical radioactive/radiolabelled substances, and of auxiliary medicinal products for human use to be submitted to the Agency during the clinical trial authorization application. This guideline sets out the requirements for investigational medicinal products and auxiliary medicinal products for human use to be used in Phase I-II-III clinical trials, as well as for test and reference products to be used in bioequivalence studies. When preparing the investigational medicinal product dossier for Phase II and Phase III clinical trials, it shall be taken into account that a greater number of volunteers will be exposed to the investigational medicinal product compared to Phase I clinical trials and that the duration of exposure will be longer. Where the active substance to be used for the investigational medicinal product, obtained from a specific source, is already used in a medicinal product for human use authorized by the competent authorities, it is not necessary to submit all documents in the investigational medicinal product dossier; in such cases, a simplified investigational medicinal product dossier will be sufficient. In addition, this guideline also lists examples of changes relating to the chemical and pharmaceutical quality requirements of the investigational medicinal product. 1.3. General Considerations for All Investigational Medicinal Products All investigational medicinal products shall be manufactured in compliance with the requirements of the Good Manufacturing Practices Guideline for Manufacturers of Medicinal Products for Human Use. 1.4. Presentation of Data The investigational medicinal product dossier shall be presented in a format consistent with Module 3 of the CTD Guideline.

The applicant shall provide a commitment stating that the investigational medicinal product dossier contains the most up-to-date information available on the clinical trial at the date of submission of the application. 1.5. General Considerations For active substances or investigational medicinal products to be used in clinical trials, reference may be made to the Turkish Pharmacopoeia (European Pharmacopoeia Adaptation), the European Pharmacopoeia, the United States Pharmacopoeia, the British Pharmacopoeia and the Japanese Pharmacopoeia. Where reference is made to monographs, it shall be verified and documented by the applicant that the relevant monograph is suitable for controlling the quality of the active substance or the finished

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product. For the active substance, compliance with the European Pharmacopoeia may be demonstrated by means of a Certificate of Suitability to the European Pharmacopoeia (CEP). Since the Certificate of Suitability to the European Pharmacopoeia (CEP) is assessed as replacing the relevant sections specified in this guideline, information that is not covered by the certificate but is required to be submitted under this guideline shall be submitted additionally. The Certificate of Suitability to the European Pharmacopoeia (CEP) does not replace batch analysis or the GMP certificate. For the active substance, reference may be made to the Active Substance Master File (ASMF). In this case, the entire ASMF (the open and closed sections in the ASMF and the Quality Overall Summary) shall be submitted. If the active substance used is already authorized in a medicinal product for human use by the competent authorities, reference may be made to this authorization, which remains valid. In this case, the marketing authorization holder or the active substance manufacturer shall submit a letter of commitment stating that the active substance to be used in the investigational medicinal product is of the same quality as the active substance used in the referenced medicinal product for human use. In addition, the name of the medicinal product for human use, the authorization number, the marketing authorization holder and the country that granted the authorization shall be specified. Apart from the situations specified above, the information and documents demonstrating that the requirements specified in this guideline have been fulfilled shall be submitted within the investigational medicinal product dossier for active substances or investigational medicinal products to be used in clinical trials. 1.6. Definitions Analytical procedure: All steps followed in performing the analysis (a detailed description of matters such as the equipment and consumables to be used; the preparation of the sample, reference standards and other reagents; calculation formulas, etc.), Analytical method: The fundamental principle of the method used in performing the analysis (e.g., GC-MS), Investigational medicinal product: A medicinal product for human use that is tested or used as a reference, including placebo, in a clinical trial, Investigational Medicinal Product Dossier (IMPD): The document containing information on the quality, manufacture and control of the investigational medicinal product, together with the data obtained from non-clinical studies and from its clinical use, including clinical trials, Active Substance Master File (ASMF): The dossier containing active substance information prepared in accordance with the Guideline on Active Substance Master File Procedure (CPMP/QWP/227/02) and the Guideline on Summary of Requirements for Active Substances in the Quality Part of the Dossier (CHMP/QWP/297/97), Pharmacopoeia: The Turkish Pharmacopoeia (European Pharmacopoeia Adaptation), the European Pharmacopoeia, the United States Pharmacopoeia, the British Pharmacopoeia and the Japanese Pharmacopoeia; and in cases where these pharmacopoeias are not applicable, the pharmacopoeia deemed appropriate by the Agency,

Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), Modified Licensed Investigational Medicinal Product: a medicinal product for human use that has been licensed by the competent authorities and for which changes have been made to the particulars on the basis of which the licence was granted, Unmodified Licensed Investigational Medicinal Product: a medicinal product for human use that has been licensed by the competent authorities and for which no changes have been made to the particulars on the basis of which the licence was granted, Common Technical Document (CTD): the internationally agreed format for the orderly presentation of applications to be submitted to the licensing authorities of the three ICH regions, namely Europe, the United States and Japan, Competent Authority: together with the Turkish Medicines and Medical Devices Agency (TİTCK), the ICH (International Council for Harmonisation) founding member competent authorities (the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), the Japan Pharmaceuticals and Medical Devices Agency (PMDA)) or the standing member competent authorities (the National Medicines Authority of Switzerland (Swissmedic) and the National Medicines Authority of Canada (Health Canada)), the National Medicines Authority of Australia (TGA) or the National Medicines Authority of the United Kingdom (MHRA), shall mean. 2. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL

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QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS 2.S Active Substance 2.S.1 General Information 2.S.1.1 Nomenclature Information on the nomenclature of the active substance (e.g. INN name, pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other names or codes, if any) should be specified. Where radionuclides or radioactively labelled substances are used in Phase I clinical trials for the development of a non-radioactive medicinal product for human use, the radionuclide or radioactively labelled substance should also be specified. For radionuclides, the isotope type (IUPAC nomenclature) should be specified. Where a radionuclide generator is concerned, both the parent radionuclide and the daughter radionuclide are regarded as active substances. For radioactively labelled kits, in addition to the radioactively labelled product, the formulation part that will carry or bind the radionuclide should be specified. For organic chemical precursors, the same information as that submitted for active substances should be provided. For active substances in herbal medicinal products (herbal drug or herbal preparation), the binomial scientific name of the plant (genus, species, variety and author) together with its chemotype, the parts of the plant used, the definition of the herbal material, its other names (synonyms appearing in other Pharmacopoeias) and the laboratory code should be specified. For herbal preparations, in addition, the ratio of the herbal drug to the herbal preparation (DER: drug extract ratio) and the extraction solvent(s) used for extraction should be specified. 2.S.1.2 Structure The data available, depending on the stage of development of the investigational medicinal product, should be submitted. To the extent they can be elucidated, these data should include the structural formula, molecular weight, chirality and stereochemical information. Where radionuclides or radioactively labelled substances are used in Phase I clinical trials for the development of a non-radioactive medicinal product for human use, the structural formula before, and if known after, radioactive labelling should be provided. For kits of radiopharmaceutical preparations, the structural formula of the ligand before, and if known after, radioactive labelling should be provided.

In addition, for active substances in herbal medicinal products (herbal drug or herbal preparation), the physical state, the type of extract and, if known, the compound(s) responsible for the therapeutic activity or the analytical markers used should be specified. 2.S.1.3 General Properties A list of the physicochemical and other relevant properties of the active substance should be submitted. The list submitted should include properties such as solubility, pKa, polymorphism, isomerism, log P and permeability that may affect pharmacological or toxicological safety. For radionuclides, the nuclear and radiophysical properties, including the sources (such as whether they derive from fission), should be specified. 2.S.2 Manufacture 2.S.2.1 Manufacturer(s) The name, address and responsibility of each manufacturer, including contractors, and of each manufacturing site or facility responsible for production, testing and batch release should be specified. Where radionuclides or radioactively labelled substances are used in Phase I clinical trials for the development of a non-radioactive medicinal product for human use, the manufacturers should be specified. For radiopharmaceuticals; together with the manufacturers of the radiopharmaceutical precursors and non-radioactive precursors, the source of the cyclotron irradiation target materials and the manufacturing site(s) where the irradiation takes place should be specified. 2.S.2.2 Description of the Manufacturing Process and Process Controls For chemical active substances; a brief summary of the synthesis process, together with a flow chart of the successive steps, including the starting materials used for each step, intermediates, solvents, catalysts and critical reagents, should be submitted. The active substance manufacturing process should be described to an extent that allows an understanding of how impurities arise and why the proposed control strategy is appropriate. This description should also include multiple chemical transformation steps. All relevant process controls should be specified. Where critical steps in the synthesis are identified, a more detailed description should be submitted. Where applicable, the stereochemical properties of the starting materials should be specified. For radionuclides; the manufacturing process and the nuclear reactions, including possible undesired nuclear reactions, should be described. The irradiation conditions should be specified. For radiopharmaceutical

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preparations and organochemical precursors, the cleaning and separation (segregation) processes should be specified. For active substances in herbal medicinal products (herbal drug or herbal preparation); a brief summary of the manufacturing process, together with a flow chart of the manufacturing steps starting from the cultivation and collection of the plant, should be submitted. The flow chart should specify the in-process controls and the main manufacturing steps. 2.S.2.3 Control of Materials A brief summary should be listed of the quality and control of the materials (e.g. raw materials, starting materials, solvents, reagents, catalysts) used in the manufacture of the active substance, together with any property anticipated to be critical. For radionuclides, details concerning the target material should be provided. 2.S.2.4 Control of Critical Steps and Intermediates Where there are critical steps in the synthesis, the tests performed for the control of these critical steps and the acceptance criteria should be briefly specified.

2.S.2.5 Process Validation and/or Evaluation Not applicable to active substances to be used in clinical trials. 2.S.2.6 Manufacturing Process Development Where the manufacturing process differs from the manufacturing process of the batches used in the non-clinical studies, this should be documented. In this case, a flow chart of the manufacturing process of the active substance used in the non-clinical studies should be submitted. For all changes made to the manufacturing process, justifications for the change should be submitted and the impact of the change on quality should be discussed. 2.S.3 Characterisation 2.S.3.1 Elucidation of Structure and Other Characteristics The structure of chemically defined active substances should be determined by appropriate methodology and the relevant data should be submitted. Non-radioactive analogue substances should be used in the structural determination of radiopharmaceutical substances. For radiopharmaceutical kits, where possible, the structure of the radioactively labelled compound should be elucidated. For herbal drugs, information on botanical, macroscopic, microscopic, phytochemical characterisation and biological activity should be provided. For herbal preparations, information on physical and phytochemical characterisation and biological activity should be provided. 2.S.3.2 Impurities For active substances compliant with a monograph of the Turkish Pharmacopoeia (European Pharmacopoeia Adaptation), the European Pharmacopoeia, the United States Pharmacopoeia, the British Pharmacopoeia and the Japanese Pharmacopoeia, reference to the relevant monographs is accepted and there is no need to submit further detail. Where reference to one of the aforementioned pharmacopoeial monographs cannot be made, the impurities relating to the active substance used in the clinical trial arising from the manufacturing process or from the starting materials (e.g. degradation products, residual solvents) should be specified. When submitting impurities, taking into consideration also the phase of the clinical trial, a description should be provided, in compliance with international standards, covering the structure, origin and justification of the limits for all impurities, including potential mutagenic impurities. Where routine control is not carried out for the solvents or catalysts used in the manufacturing process, this should be justified. Where radionuclides or radioactively labelled substances are used in Phase I clinical trials for the development of a non-radioactive medicinal product for human use, the radiochemical purity and the chemical purity should be specified, with an explanation of the assumptions made (e.g. the result of the assay performed before dilution with cold material). For radiopharmaceutical substances, details on radionuclidic purity, radiochemical purity and chemical purity should be provided. For active substances in herbal medicinal products (herbal drug or herbal preparation); data on potential contamination by microorganisms, products of microorganisms, aflatoxins, pesticides, toxic metals, radioactive contamination, fumigants, etc. should be specified. The general requirements of the aforementioned pharmacopoeias should be met.

2.S.4 Control of Active Substance 2.S.4.1 Specifications The specifications for the batches of active substance(s) used in the clinical trial, the tests used, and their acceptance criteria shall be specified. Identification, impurity, and assay tests are mandatory. Safety data shall be taken into consideration when establishing upper limits for impurities. The limits shall be supported by the impurity profiles of the active substance batches used in nonclinical and clinical trials. Where ICH

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guidelines or Pharmacopoeial requirements are met for the limits, no further justification is expected to be submitted. The information provided in international guidelines shall be taken into consideration when establishing specifications for potentially mutagenic impurities. For active substances used in products manufactured under aseptic conditions, microbiological quality shall be specified in the specifications. Acceptance criteria for residual solvents and catalysts shall be included in the specifications. For radiopharmaceutical active substances, the levels of radionuclidic impurities, radiochemical impurities, and chemical impurities shall be specified. Additional Information for Phase II and Phase III Clinical Trials The specifications and acceptance criteria established during the drug development stages may need to be reviewed and rearranged. 2.S.4.2 Analytical Procedures Analytical methods shall be specified for all tests included in the specifications of the active substance (e.g., reversed-phase HPLC-UV, potentiometric titration, head-space GC-FID, etc.). It is not necessary to provide analytical procedures in detail. For radiopharmaceutical active substances, the analytical method used for the measurement of radioactivity shall be specified. For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. 2.S.4.3 Validation of Analytical Procedures Information for Phase I Clinical Trials The suitability of the analytical methods used shall be declared. Analytical method validation parameters (specificity/selectivity, linearity, working range, accuracy, precision, and where required, limit of quantification and limit of detection) and acceptance limits shall be presented in tabular format. Information for Phase II and Phase III Clinical Trials The suitability of the analytical methods used shall be demonstrated. It will be sufficient to present the analytical method validation results (e.g., the results or values found for specificity/selectivity, linearity, working range, accuracy, precision, and where required, limit of quantification and limit of detection) in the form of a summary table. It is not necessary to submit a full validation report. For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. In cases where major changes are made to analytical methods, cross-validation results shall be submitted, unless otherwise specified, in particular for unknown impurities with specifications defined by relative retention time (RRT). Where relevant, re-analysis of the nonclinical batch using the new analytical method should also be considered.

2.S.4.4 Batch Analyses Certificates of analysis or batch analysis results in tabular format for the batches to be used in the current clinical trial and for the batches used in nonclinical studies shall be submitted. Furthermore, in cases where the batches to be used in the current clinical trial phase have a different manufacturing process from the batches used in previous phases, certificates of analysis for representative batches used in previous phases or batch analysis results in tabular format shall be submitted in order to demonstrate that the quality characteristics are comparable. If data regarding the batches to be used in the current clinical trial are not available, data for representative batches from each active substance manufacturer may be submitted instead. Batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria, and test results shall be listed. The manufacturing process used for each batch shall be specified as described in Section 2.S.2.2. 2.S.4.5 Justification of Specifications For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. For active substances for which no reference can be made to a pharmacopoeial monograph, a brief justification of the specifications and acceptance criteria for impurities and other parameters that may affect the performance of the finished product shall be submitted in accordance with international guidelines. This justification shall also be based on safety and toxicity data. Solvents and catalysts used in the synthesis shall also be taken into consideration. 2.S.5 Reference Standards or Materials Where applicable, the parameters characterizing the active substance batch designated as the reference standard shall be submitted. For radiopharmaceuticals, data on the standards used for calibration and on non-radioactive (cold) standards shall be submitted. For herbal preparations, the parameters characterizing primary reference standards shall be submitted. Where a herbal drug is not defined in a monograph of the

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pharmacopoeia, a certified herbarium specimen of the herbal drug shall be available. 2.S.6 Container Closure System The primary packaging material used for the active substance shall be specified. In cases where non-standard (not included in the Pharmacopoeia) materials are used, the description and specifications of such materials shall be submitted. 2.S.7 Stability The stability data available for the relevant clinical trial phase shall be summarized in tabular format. Stability data shall be submitted for batch(es) manufactured by a representative process (a manufacturing process with the same or very similar synthesis and comparable batch size). These stability data shall be supported by data obtained from batch(es) manufactured by previous processes. The re-test period shall be defined based on the available stability data and clearly stated. Alternatively, for active substances within the scope of a pharmacopoeial monograph, a commitment stating that the active substance will meet the specifications at the time of use shall be submitted.

For active substances holding a Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) for which the re-test period is not specified on the document, supporting stability data and the re-test period shall be submitted. In cases where the re-test period is not specified, a declaration stating that the active substance has been tested immediately prior to the manufacture of the finished product shall be submitted. Where the stability protocol, the re-test period extension plan, and a declaration that the applicant will inform the Agency and the relevant ethics committee in the event of detection of any significant negative trend are submitted, the re-test period may be extended without the need for a major variation application. The stability protocol shall cover the planned maximum re-test period. For herbal preparations, stress test results may not be submitted, provided that this is justified. 2.P Clinical Trial Product 2.P.1 Description and Composition of the Clinical Trial Product The complete qualitative and quantitative composition of the clinical trial product shall be specified. The dosage form and the function of each excipient shall be presented in tabular format with a brief description. For dosage forms, the Standard Terms List of the European Pharmacopoeia should preferably be used. Additionally, for radiopharmaceuticals, the radioactivity per unit shall be specified. Where appropriate, the radioactivity shall be expressed only in Becquerel at the date and time given. If a calibration time is specified, the time zone used shall be stated (e.g., GMT-Greenwich Mean Time/CET-Central European Time). 2.P.2 Pharmaceutical Development A brief description of formulation development shall be submitted, including the justification of any new pharmaceutical form or excipient. In the early stages of drug development, the information to be included in this section may be limited. The components of the investigational product, the dosage form, and the administration device, if any, shall be safe and suitable for the patient population. Where applicable; the compatibility of the investigational product with the solvents, diluents, and additives used for reconstitution shall be demonstrated. For products to be reconstituted or diluted prior to use, the method of preparation shall be summarized and reference shall be made to the full instructions included in the trial protocol or to the relevant instructions for use to be available at the clinical trial site. For kits of radiopharmaceutical preparations, it shall be demonstrated that the method used for radioactive labelling is suitable for the intended use (including results on the physiological distribution after radioactive labelling in rats/rodents). For radionuclide generators, the suitability of the elution medium shall be demonstrated. For radiopharmaceuticals, the effect of radiolysis on purity shall be specified. Additional Information for Phase II and Phase III Clinical Trials Where changes have been made to the formulation or dosage form when the investigational product to be used in the current clinical trial is compared with the investigational product used in previous clinical trial phases, the suitability shall be explained taking into consideration the impact of such change on clinical efficacy. 2.P.2.1 Manufacturing Process Development Where changes have been made to the manufacturing process when the investigational product to be used in the current clinical trial is compared with the investigational product used in previous clinical trial phases, the suitability shall be explained taking into consideration the impact of such change on clinical efficacy.

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2.P.3 Manufacture 2.P.3.1 Manufacturer(s) For investigational medicinal products to be used in the clinical trial, the name(s), address(es) and responsibilities of all manufacturer(s), including contractors, and of each manufacturing site to be involved in the manufacturing, packaging/assembly and testing stages should be specified. In cases where the investigational medicinal product is to be repackaged or relabelled at trial sites that do not hold a "manufacturing site licence" and where it will be used exclusively for that trial, the relevant provision requirements of the Good Manufacturing Practices (GMP) Guide for Human Medicinal Products Manufacturing Facilities should be taken into consideration. It should be stated in this section that these activities will be carried out. 2.P.3.2 Batch Formula The batch formula and batch size of the batch(es) to be used in the clinical trial should be provided. 2.P.3.3 Description of Manufacturing Process and Process Controls A flow diagram and a brief description of the manufacturing process should be provided for consecutive manufacturing steps, indicating the components used at each manufacturing step and the relevant in-process controls. Non-standard manufacturing processes, novel technologies or new packaging processes should be described in more detail. 2.P.3.4 Control of Critical Steps and Intermediates For Phase I and II clinical trials, no information is required other than the following: - Non-standard manufacturing processes and - Manufacturing process for sterile products In the application dossier, the maximum acceptable bioburden prior to filtration should be specified for sterilising filtration. Depending on the volume to be filtered in relation to the filter diameter, NMT 10 CFU/100 ml is often sufficient. If this criterion cannot be met, pre-filtration with a bacteria-retentive filter should be performed in order to achieve a sufficiently low bioburden value. If the quantity of the formulated investigational medicinal product is limited, a pre-filtration/filtration volume of less than 100 ml may be tested, provided that it is justified. A statement should be provided that the aseptic process has been validated using media fill runs. Additional information for Phase III clinical trials If critical manufacturing steps have been identified; their controls and possible intermediates should be specified. In case intermediates are stored, a statement should be provided that the storage time and conditions are appropriately controlled. 2.P.3.5 Process Validation and/or Evaluation Not applicable for investigational medicinal products to be used in Phase I, Phase II and Phase III clinical trials. However, where sterilisation procedures not included in the Pharmacopoeia (non-standard) are applied, the critical manufacturing steps, the validation of the manufacturing process and the process controls applied should be provided.

2.P.4 Control of Excipients 2.P.4.1 Specifications References to the Pharmacopoeia should be specified. For mixtures of excipients composed of substances included in the Pharmacopoeia (e.g., ready-prepared (prefabricated) dry mixtures for film coating), it is sufficient to provide general specifications for the mixture. For excipients not included in the Pharmacopoeia, an in-house monograph should be provided. A specification should be provided for the capsule shell. 2.P.4.2 Analytical Procedures Where reference to a pharmacopoeial monograph cannot be made, the analytical methods used should be specified. 2.P.4.3 Validation of Analytical Procedures Not applicable. 2.P.4.4 Justification of Specifications Not applicable. 2.P.4.5 Excipients of Human or Animal Origin See Section 7.A.2. 2.P.4.6 Novel Excipients For novel excipients, detailed information should be provided on the manufacturing process, characterisation and controls related to product safety. In accordance with the relevant phase of the clinical trial, the information specified in section 3.2.S of the CTD should be provided (see section 7.A.3); for example, information on the manufacturing process, characterisation and stability should be included. 2.P.5 Control of the Investigational Medicinal Product 2.P.5.1 Specifications The release and shelf-life specifications for the batches of the investigational medicinal product to be used in the clinical trial, the tests used and their acceptance criteria should be specified. Identification, degradation products and assay tests are mandatory. Upper limits should be set for each degradation product and for total degradation products. Safety information should be taken into account when setting the upper limits. The limits should be supported by the impurity profiles of the active substance batches used in non-clinical and clinical trials. During the stages of drug development, the established

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specifications and acceptance criteria may need to be reviewed and revised. Depending on the pharmaceutical form, tests specific to the finished product (e.g., dissolution/disintegration for oral solid dosage forms; uniformity of dosage units or pH, bacterial endotoxins and sterility tests for parenteral dosage forms) and the acceptance criteria should be included in the specifications. In cases where tests specific to the finished product are not included in the specifications, this should be justified. For radiopharmaceuticals, it should be specified which tests are performed prior to batch release and which tests are performed retrospectively. For kits of radiopharmaceutical preparations, the appropriate tests after radioactive labelling should be specified. For medicinal products to be reconstituted or diluted prior to use, the acceptable quality characteristics after preparation should be specified.

Additional Information for Phase II and Phase III Clinical Trials The specifications and acceptance criteria established during Phase I and Phase II clinical trials may need to be reviewed and revised. 2.P.5.2 Analytical Procedures For all tests included in the specifications of the finished product (e.g., the dissolution test method), analytical methods should be specified. It is not necessary to provide the analytical procedures in detail. For methods compliant with the pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. 2.P.5.3 Validation of Analytical Procedures Information for Phase I Clinical Trials The suitability of the analytical methods used is declared. Analytical method validation parameters (specificity/selectivity, linearity, working range, accuracy, precision and, where required, limit of quantification and limit of detection) and acceptance limits should be presented in tabular form. Information for Phase II and Phase III Clinical Trials The suitability of the analytical methods used should be demonstrated. It is sufficient to present the analytical method validation results (e.g., the results or values obtained for specificity/selectivity, linearity, working range, accuracy, precision and, where required, assay and detection limit) in the form of a summary table. It is not necessary to provide a full validation report. For methods compliant with the pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. 2.P.5.4 Batch Analysis Certificates of analysis or batch analysis results in tabular form should be provided for batch(es) representative of the batch to be used in the clinical trial (batches manufactured at the same manufacturing site with the same manufacturing process, the same composition and a comparable batch size). The results should cover all batches to be used in the clinical trial. Batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria and test results should be listed. In the case of more than one bulk manufacturing site, batch analysis results should be provided for the bulk product manufactured at each bulk manufacturing site and for the batches of the investigational medicinal product manufactured from it. Results of previous batches controlled according to wider specifications may be accepted if the results comply with the specifications established for the current clinical trial. 2.P.5.5 Characterisation of Impurities Additional impurities/degradation products not covered by section 2.S.3.2 but observed in the investigational medicinal product should be specified. 2.P.5.6 Justification of Specifications Information for Phase I Clinical Trials For finished products used in the clinical trial, a brief justification of the specifications for degradation products and of the specifications and acceptance criteria for other parameters that may affect the performance of the finished product should be provided in accordance with international guidelines. This justification should also be based on safety and toxicity data.

Additional Information for Phase II and Phase III Clinical Trials The selection of specifications and acceptance criteria for parameters that may affect efficacy or safety shall be justified in accordance with international guidelines. 2.P.6 Reference Standards or Materials In cases where a pharmacopoeial reference standard is not available, the parameters required for the characterisation of the reference standard shall be submitted. Where applicable, reference may be made to section 2.S.5 Reference Standards or Materials. For radiopharmaceuticals, information shall be submitted on the radioactive standards used in the calibration of the radioactivity measurement equipment. 2.P.7 Container Closure System The primary packaging material to be

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used for the investigational medicinal product shall be specified. In addition, in cases where the secondary packaging material affects the quality of the finished product, the secondary packaging shall also be specified in addition to the primary packaging. Where available, reference shall be made to the pharmacopoeial monograph. If the investigational medicinal product is packaged in a non-pharmacopoeial (non-standard) administration device, or if non-pharmacopoeial (non-standard) packaging materials are used, the packaging description and specifications shall be provided. For dosage forms with a high potential for interaction between the fill and the container closure system (e.g., parenterals, ophthalmic products, oral solutions), more detail (e.g., extractables, leachables) may need to be submitted within the scope of Phase III clinical trials. However, in cases where interaction is unlikely, such as solid oral dosage forms, information may not be submitted. If a medical device is to be used for the administration of the investigational medicinal product, its legal status shall be clearly specified (e.g., whether or not it bears CE marking for its intended use). In the absence of a certificate for the intended use, a declaration shall be submitted stating that the medical device complies with the relevant legal requirements concerning safety and performance requirements. In cases where a medicinal product is integrally combined with a medical device and the principal effect lies with the medicinal product, this integrated product is subject to pharmaceutical legislation and CE marking is not required during development. However, in the marketing authorisation application for the medicinal product, the requirements of paragraph 2 of Article 3 of Section I set out in Annex-1 of the Regulation on Licensing of Medicinal Products for Human Use, published in the Official Gazette No. 31686 dated 11/12/2021, shall apply. 2.P.8 Stability The shelf life and storage conditions of the investigational medicinal product shall be determined on the basis of the stability profile of the active substance and the available data on the investigational medicinal product. Stability data for the representative batch(es) shall be presented in table form. Provided that an appropriate justification regarding the representativeness of the quality of the investigational medicinal product is submitted, data from such batches may be used in determining the shelf life of the finished product. Extrapolation may be carried out on condition that the stability studies are conducted in parallel with the clinical trial and throughout the entire duration of the clinical trial. Shelf life extrapolation may be performed under the following conditions: - Results under both long-term and accelerated storage conditions shall be available, - No significant change shall be observed in the stability results; in cases where any significant change is observed, a justification thereon shall be submitted, - The stability protocol shall cover the proposed extrapolated shelf life, - The criteria determined for extrapolation shall be clearly specified, and

- Based on the available data; - For shelf lives of up to 12 months, extrapolation of up to 4 (four) times the accelerated stability data may be acceptable. - For shelf lives of 12 months and above, provided that there are at least 6 (six) months of long-term stability data, extrapolation of the available long-term stability data by a maximum of +12 months may be acceptable. In addition, provided that it is justified, bracketing and matrixing designs may be acceptable for suitable investigational medicinal products. The investigational medicinal product batches shall meet the specification requirements throughout their periods of use. In case a problem arises in this respect, a notification concerning this matter, including the proposed corrective actions, shall be submitted to the Agency and the relevant ethics committee. Where the investigational medicinal product is stored in bulk for a significant period of time, information on the shelf life, storage conditions and packaging material of the bulk product, together with the relevant stability data for the bulk product, shall also be submitted. Where the shelf life of the finished product is calculated not from the moment the active substance and excipients are first mixed, but from the moment primary packaging is performed, this shall be clearly stated and justified. If there is a plan for future shelf life extensions, this plan shall be specified in the investigational medicinal product dossier. The stability protocol shall include the shelf life extension plan and a declaration stating that the applicant will inform the Agency and the relevant ethics committee in the event of any significant negative trend. The stability protocol shall cover the planned maximum shelf life. For

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investigational medicinal products administered after reconstitution, dilution or mixing, and for investigational medicinal products containing multiple doses, in-use stability data shall be submitted. In-use stability studies shall cover the administration specified in the clinical trial protocol. The shelf life and storage conditions after first opening and/or reconstitution and/or dilution shall be specified. If the investigational medicinal product is to be used immediately after opening or reconstitution, and it can be justified that there will be no adverse effect on the stability of the investigational medicinal product, in-use stability studies are not required. For radiopharmaceuticals, since stability also depends on the half-life of the radioactive isotope, the calibration time shall be specified. Information for Phase I Clinical Trials For Phase I clinical trials; before the start of the trial, initial data from stability studies under at least accelerated and long-term storage conditions for the batch(es) of the investigational medicinal product to be used in the clinical trial shall be submitted, and it shall be declared that the stability studies will continue with the relevant batch(es) in accordance with the protocol. Data from stability studies conducted with the batch(es) to be used in the clinical trial and with representative batches shall be summarised in table form. An evaluation of the available data and a justification for the proposed shelf life of the investigational medicinal product shall be submitted. Additional Information for Phase II and Phase III Clinical Trials

The available stability data shall be presented in table form. An evaluation of the available data and a justification for the proposed shelf life of the investigational medicinal product to be used in the clinical trial shall be submitted. The data shall include the results obtained from studies under accelerated and long-term storage conditions. For radiopharmaceuticals, the calibration time shall be specified. For ready-to-use radiopharmaceuticals, radionuclide generators and radioactive precursors, the matters specified in the Guideline on Radiopharmaceuticals (EMEA/CHMP/QWP/306970/2007) shall be taken into consideration. 3. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS AUTHORISED BY THE COMPETENT AUTHORITIES WITH NO MODIFICATION MADE TO THE INFORMATION SUPPORTING THE MARKETING AUTHORISATION (UNMODIFIED) Where the test and comparator products to be used in the clinical trial are authorised by the competent authorities; it will be sufficient to submit the name of the marketing authorisation holder and the licence number (including equivalent information such as a copy of the Short Product Information / the Summary of Product Characteristics or prescribing information). For modified authorised investigational medicinal products, see the following section (Section 4). For unmodified authorised investigational medicinal products, a declaration that the investigational medicinal product will be used in accordance with the expiry date determined by the manufacturer is sufficient. Where only repackaging is carried out without changing the primary packaging, in addition to the requirements listed in Section 3 of the Guideline on the Chemical and Pharmaceutical Quality Requirements for Medicinal Products for Human Use Used in Clinical Trials, the following information shall be included in the simplified investigational medicinal product dossier: - Information guaranteeing that the investigational medicinal product has the appropriate identity, assay, quality and purity characteristics (e.g., for investigational medicinal products authorised by the competent authorities, reference to the Short Product Information), - Information on the facility where the repackaging/relabelling operations are carried out. For test and comparator products not authorised by the competent authorities, a complete application shall be submitted in accordance with the requirements specified in Section 2 of this guideline. 4. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF INVESTIGATIONAL MEDICINAL PRODUCTS AUTHORISED BY THE COMPETENT AUTHORITIES WITH MODIFICATION MADE TO THE INFORMATION SUPPORTING THE MARKETING AUTHORISATION (MODIFIED) Where there is blinding within the scope of the clinical trial protocol, applicants usually modify or manipulate the test and comparator products to be used in the clinical trial. The applicant shall declare that the modifications made to the test and comparator products to be used in the clinical trial do not adversely affect the quality of the product, and the necessary information and documents shall be submitted with emphasis on the

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biopharmaceutical characteristics. For test and comparator products not authorised by the competent authorities, a complete application shall be submitted in accordance with the requirements specified in Section 2 of this guideline. 4.P Modified Authorised Investigational Medicinal Product 4.P.1 Description and Composition Where any modification is made to a medicinal product for human use authorised by the competent authorities, except for repackaging, the qualitative and quantitative composition of the authorised medicinal product for human use

should be specified. The licensed name of the product authorized by competent authorities, the authorization number and the competent authority granting the authorization should be specified. All additional substances/materials added to the product authorized by competent authorities should be listed, making reference to pharmacopoeial or in-house monographs. 4.P.2 Pharmaceutical Development The modifications made to the product authorized by competent authorities and the effects of these modifications on the quality of the product should be described. Depending on the modification, all parameters that may be relevant to the function, stability and efficacy of the human medicinal product (such as in vitro dissolution and pH value) should be described. It should be demonstrated that these parameters are comparable with those of the unmodified licensed product. In cases where the finished product is reconstituted or diluted with a different solvent not specified in the original Summary of Product Characteristics or Package Leaflet, compatibility with these solvents should be demonstrated. In cases where there are special applications not specified in the original Summary of Product Characteristics or Package Leaflet of the finished product but specified in the clinical trial protocol (e.g. dispersion of a tablet or the contents of a hard capsule in water/fruit juice/food), compatibility with such applications should be demonstrated. In the case of solid oral dosage forms, comparative dissolution profiles of the modified licensed product and the human medicinal product authorized by competent authorities should be submitted in order to ensure that the biopharmaceutical properties have not changed. In cases where comparability cannot be demonstrated in vitro, additional clinical data may be requested to support equivalence. 4.P.3 Manufacture 4.P.3.1 Manufacturer(s) Responsible for the Modification For modified licensed investigational products, the name(s), address(es) and responsibilities of all manufacturer(s), including contractors, and of each manufacturing site to be involved in the modification, packaging/assembly and testing stages should be specified. In cases where the investigational product is re-packaged or re-labelled at trial sites that do not hold a "manufacturing site authorization" for use exclusively in the trial, the relevant provision requirements of the Good Manufacturing Practices (GMP) Guide for Manufacturers of Human Medicinal Products should be taken into consideration. It should be stated in this section that these activities will be carried out. 4.P.3.2 Batch Formula The batch formula of the batch to be used in the clinical trial should be submitted. This section is not applicable for modified licensed investigational products that have only been re-packaged. 4.P.3.3 Description of Manufacturing Process and Process Controls All modification steps of the product authorized by competent authorities, including process controls, should be described. For details, see Section 2.P.3.3

4.P.4 Control of Excipients 4.P.4.1 Specifications References to the pharmacopoeia should be specified. For mixtures of excipients composed of substances included in the pharmacopoeia (e.g. ready-made dry mixture for film coating), it is sufficient to submit general specifications for the mixture. For excipients not included in the pharmacopoeia, an in-house monograph should be submitted. Specifications should be submitted for the capsule shell. 4.P.4.2 Analytical Procedures In cases where reference cannot be made to a pharmacopoeial monograph, the analytical methods used should be specified. 4.P.4.3 Validation of Analytical Procedures Not applicable. 4.P.4.4 Justification of Specifications Not applicable. 4.P.4.5 Excipients of Human or Animal Origin See Section 7.A.2. 4.P.5 Control of the Modified Licensed Investigational Product 4.P.5.1 Specifications The release and shelf life specifications of the modified licensed investigational product, the tests used and their acceptance criteria should be specified. In general, the specifications should include tests for the identification and appearance of the active substance, as well as tests for the control of important pharmaceutical and technological characteristics such as

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dissolution. In cases where an intact solid oral dosage form that can be easily recognized by its colour, shape and marking is encapsulated, an identification and appearance test for the active substance may not be necessary and visual inspection may be sufficient for identification. Depending on the degree of modification of the product authorized by competent authorities, additional quality attributes, such as the assay of the active substance(s) and the determination of impurities/degradation products, may need to be specified in the specifications and tested. 4.P.5.2 Analytical Procedures Analytical methods should be specified for all tests relating to the performance of the modified licensed investigational product (e.g. dissolution test). It is not necessary to provide the analytical procedures in detail. 4.P.5.3 Validation of Analytical Procedures The suitability of the analytical methods used should be demonstrated. It is sufficient to submit the results of the analytical method validation (e.g. the results or values found for specificity/selectivity, linearity, working range, accuracy, precision and, where required, the limit of quantification and the limit of detection) in the form of a summary table. There is no need to submit a full validation report. 4.P.5.4 Batch Analysis Certificates of analysis or batch analysis results in tabular form should be submitted for the batches of the modified licensed investigational product to be used in the relevant clinical trial, or for representative batches.

Batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria and test results should be listed. In cases where there is more than one bulk manufacturing site, batch analysis results should be submitted for the bulk product manufactured at each bulk manufacturing site and for the batches of the modified licensed investigational product manufactured from them. 4.P.5.5 Characterisation of Impurities In cases where the sponsor has made a significant modification that may affect the stability of the product authorized by competent authorities, it should be demonstrated that the impurity profile has not changed compared to the product authorized by competent authorities. In cases where the sponsor has made a minor modification at a level that will not affect the stability of the product authorized by competent authorities, the amounts of impurities may not be specified; however, this should be justified. 4.P.5.6 Justification of Specifications In cases where the sponsor has made a significant modification that may affect the performance or safety of the product authorized by competent authorities, the specification(s) should be justified. 4.P.7 Container Closure System The type and material of the primary packaging and the packaging size(s) should be specified. If materials different from the primary packaging of the product authorized by competent authorities are used, a description of these materials and the specifications of the relevant packaging material should be submitted. Where available, reference should be made to a pharmacopoeial monograph. If the modified licensed investigational product is packaged in a (non-standard) administration device not included in the pharmacopoeia, or if (non-standard) packaging materials not included in the pharmacopoeia are used, the packaging description and specifications should be provided. 4.P.8 Stability In cases where the sponsor has made a significant modification that may affect the stability of the product authorized by competent authorities, minimum stability data for the modified licensed product should be available before the start of the clinical trial and depending on the duration of the planned clinical trial, in order to allow assessment of the impact of the modification made on the safety and stability of the product. The available stability data should be presented in tabular form. An evaluation of the available data and a justification for the proposed shelf life of the investigational product should be submitted. The shelf life extrapolation made for the modified licensed investigational product shall not exceed the shelf life of the product authorized by competent authorities. Issues relating to future shelf life extensions are set out in Section 2.P.8. Where only minor modifications are involved, justification of stability throughout the expected duration of the trial is acceptable. In cases where, according to the clinical trial protocol, the modified licensed investigational product is used under conditions other than those specified in the Summary of Product Characteristics, in-use stability studies should be performed. Issues relating to these studies are set out in Section 2.P.8.

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5. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF TEST PRODUCTS CONTAINING ACTIVE SUBSTANCES OF LICENSED PRODUCTS AND TO BE USED IN BIOEQUIVALENCE STUDIES (GENERICS (CHEMICAL SUBSTANCES)) This section of the guideline concerns only the test products to be used in bioequivalence studies. For reference products authorized by competent authorities, a complete submission should be provided in accordance with the requirements set out in Sections 3 and 4 of this guideline; for reference products not authorized by competent authorities, a complete submission should be provided in accordance with the requirements set out in Section 2 of this guideline. In cases where the relevant bioequivalence study is designed within the scope of a marketing authorization application in Türkiye, the provisions of the Guideline on the Investigation of Bioavailability and Bioequivalence of Human Medicinal Products should be taken into consideration for the selection of the reference product to be used in bioequivalence studies. 5.S Active Substance See Section 1.5 5.S.1 General Information 5.S.1.1 Nomenclature Information on the nomenclature of the active substance (e.g. INN name, pharmacopoeial name, chemical name (IUPAC, CAS-RN), laboratory code, other names or codes, if any) should be specified. 5.S.1.2 Structure The structural formula should be submitted. 5.S.1.3 General Properties The essential physicochemical and other relevant properties of the active substance should be specified. 5.S.2 Manufacture 5.S.2.1 Manufacturer(s) The name, address and responsibility of each manufacturer, including contractors, and each manufacturing site or facility where manufacturing and testing are carried out should be specified. 5.S.2.2 Description of Manufacturing Process and Process Controls Where reference cannot be made to a pharmacopoeial monograph, a brief summary of the synthesis process and a flow chart for the consecutive steps, including starting materials, intermediates, solvents, catalysts and critical reagents used for each step, should be submitted. Where applicable, the stereochemical properties of the starting materials should be specified. 5.S.3 Characterisation 5.S.3.2 Impurities For active substances compliant with the Turkish Pharmacopoeia (European Pharmacopoeia Adaptation), the European Pharmacopoeia, the United States Pharmacopoeia, the British Pharmacopoeia and the Japanese Pharmacopoeia, reference to the relevant monographs is accepted and there is no need to provide further detail. In accordance with international standards, a description should be submitted containing the structure, origin and justification of limits for potential mutagenic impurities. In cases where reference cannot be made to one of the specified pharmacopoeial monographs, impurities (e.g. degradation products, residual solvents) arising from the manufacturing process or starting materials of the active substance used in bioequivalence studies should be specified.

Where routine testing is not performed for solvents or catalysts used in the manufacturing process, this situation should be justified.

5.S.4 Control of the Active Substance

5.S.4.1 Specifications The specifications for the active substance used in bioequivalence studies, the tests used and their acceptance criteria should be specified. Identification, impurity and assay tests are mandatory. Safety data should be taken into consideration when setting upper limits for impurities. The limits should be supported by the impurity profiles of the active substance batches used in non-clinical and clinical trials. Where ICH or Pharmacopoeial requirements are met for the limits, no further justification is expected. The information provided in international guidelines should be taken into consideration when setting specifications for potential mutagenic impurities. For active substances used in products manufactured under aseptic conditions, microbiological quality should be specified in the specifications.

5.S.4.2 Analytical Procedures The analytical methods used in the analysis of the active substance should be specified for all tests included in the specifications (e.g., reverse-phase HPLC-UV, potentiometric titration, head-space-GC-FID, etc.). It is not necessary to provide the analytical procedures in detail. For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient.

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5.S.4.3 Validation of Analytical Procedures The suitability of the analytical methods used should be demonstrated. It is sufficient to present the analytical method validation results (e.g., results or values found for specificity/selectivity, linearity, working range, accuracy, precision and, where applicable, assay and detection limit) in the form of a summary table. A full validation report does not need to be submitted. For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient.

5.S.4.4 Batch Analyses Certificates of analysis or batch analysis results in tabular form for the batches to be used in the current bioequivalence study should be submitted. If data on the batches to be used in the current bioequivalence study are not available, data from representative batches may be submitted instead. Batch number, batch size, manufacturing site, date of manufacture, control methods and test results should be listed.

5.S.4.5 Justification of Specifications For active substances compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient. For active substances for which no reference to a pharmacopoeial monograph can be made, a brief justification of the specifications and acceptance criteria for impurities and other parameters that may affect the performance of the finished product should be provided in accordance with international guidelines. This justification should also be based on safety and toxicity data. Solvents and catalysts used in the synthesis should also be taken into consideration.

5.S.5 Reference Standards or Materials For active substances for which no reference to a pharmacopoeial monograph can be made, the parameters characterising the active substance batch designated as the reference standard should be submitted.

5.S.6 Container Closure System The primary packaging material used for the active substance should be specified. Where non-standard (not included in the Pharmacopoeia) materials are used, the description and specifications of such materials should be submitted.

5.S.7 Stability The available stability data should be summarised in tables. The re-test period should be defined on the basis of the available stability data and clearly stated. For active substances holding a Certificate of Suitability to the European Pharmacopoeia (CEP) for which no re-test period is stated on the certificate, the re-test period should be specified and supporting stability data should be submitted. In cases where the re-test period is not specified, a statement should be included that the active substance is tested immediately prior to the manufacture of the finished product.

5.P Test Product

5.P.1 Description and Composition of the Test Product The complete qualitative and quantitative composition of the test product should be specified. For dosage forms, preferably the European Pharmacopoeia Standard Terms list should be used.

5.P.2 Pharmaceutical Development A brief description of the dosage form should be provided.

5.P.3 Manufacture

5.P.3.1 Manufacturer(s) For the test products to be used in the bioequivalence study, the name(s), address(es) and responsibilities of all manufacturer(s), including contractors, and of each manufacturing site involved in the manufacturing, packaging/assembly and testing stages should be specified. In cases where the test product is to be repackaged or relabelled at trial sites that do not hold a "manufacturing site authorisation" exclusively for use of the product in the trial, the relevant provisions of the Good Manufacturing Practices (GMP) Guide for Human Medicinal Products Manufacturing Facilities should be taken into consideration. It should be stated in this section that these activities will be carried out.

5.P.3.2 Batch Formula The batch formula and batch size of the batches to be used in bioequivalence studies should be submitted.

5.P.3.3 Description of Manufacturing Process and Process Controls A flow chart for the consecutive manufacturing steps and a brief description of the manufacturing process should be provided, specifying the components used at each manufacturing step and the relevant in-process

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controls.

5.P.3.4 Controls of Critical Steps and Intermediates If critical manufacturing steps have been identified; their controls and possible intermediates should be specified. Where intermediates are stored, a statement should be provided that the storage time and conditions are appropriately controlled.

5.P.3.5 Process Validation and/or Evaluation Not applicable to test products to be used in bioequivalence studies. However, in cases where non-compendial (non-standard) sterilisation processes are applied, critical manufacturing steps, validation of the manufacturing process and the process controls applied should be submitted.

5.P.4 Control of Excipients

5.P.4.1 Specifications References to the Pharmacopoeia should be specified. For mixtures of excipients composed of substances included in the Pharmacopoeia (e.g., premixed dry blends for film coating), it is sufficient to submit general specifications for the mixture. For excipients not included in the Pharmacopoeia, an in-house monograph should be submitted. For capsule shells, specifications should be submitted.

5.P.4.2 Analytical Procedures In cases where no reference to a pharmacopoeial monograph can be made, the analytical methods used should be specified.

5.P.4.3 Validation of Analytical Procedures Not applicable.

5.P.4.4 Justification of Specifications Not applicable.

5.P.4.5 Excipients of Human or Animal Origin See Section 7.A.2.

5.P.4.6 Novel Excipients For novel excipients, detailed information should be provided on the manufacturing process, characterisation and controls related to product safety. The information specified in Section 3.2.S of the CTD should be submitted in accordance with the relevant clinical trial phase (see Section 7.A.3); for example, information on the manufacturing process, characterisation and stability should be included.

5.P.5 Control of the Test Product

5.P.5.1 Specifications The release and shelf-life specifications of the test product batches to be used in the bioequivalence study, the tests used and their acceptance criteria should be specified. Identification, degradation products and assay tests are mandatory. Depending on the pharmaceutical form, product-specific tests and acceptance criteria should be included in the specifications. In cases where product-specific tests are not included in the specifications, this should be justified.

5.P.5.2 Analytical Procedures Analytical methods should be specified for all tests included in the specifications of the finished product (e.g., dissolution test method). It is not necessary to provide the analytical procedures in detail. For methods compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient.

5.P.5.3 Validation of Analytical Procedures The suitability of the analytical methods used should be demonstrated. It is sufficient to present the analytical method validation results (e.g., results or values found for specificity/selectivity, linearity, working range, accuracy, precision and, where applicable, assay and detection limit) in the form of a summary table. A full validation report does not need to be submitted. For methods compliant with a pharmacopoeial monograph, a reference to the relevant monograph will be sufficient.

5.P.5.4 Batch Analysis Certificates of analysis or batch analysis results in tabular form for the batches to be used in the current bioequivalence study should be submitted. If data on the batches to be used in the current bioequivalence study are not available, data from representative batches may be submitted instead. Batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria and test results should be listed.

5.P.5.5 Characterisation of Impurities Additional impurities/degradation products not covered by Section 5.S.3.2 but observed in the test product should be specified.

5.P.5.6 Justification of Specifications For test products used in the bioequivalence study, a brief justification of the specifications for degradation products and the specifications and

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acceptance criteria for other parameters that may affect the performance of the finished product should be provided in accordance with international guidelines. This justification should also be based on safety and toxicity data.

5.P.6 Reference Standards or Materials In cases where no pharmacopoeial reference standard is available, the parameters necessary for the characterisation of the reference standard should be submitted. Where applicable, reference may be made to Section 5.S.5 Reference Standards or Materials.

5.P.7 Container Closure System The primary packaging material to be used for the test product should be specified. In addition, where the secondary packaging material affects the quality of the finished product, the secondary packaging should also be specified in addition to the primary packaging. Where available, reference should be made to the pharmacopoeial monograph. If the test product is packaged in a non-compendial (non-standard) delivery device or if non-compendial (non-standard) packaging materials are used, the packaging description and specifications should be specified. For dosage forms with a high potential for interaction between the fill and the container closure system (e.g., parenterals, ophthalmic products, oral solutions), further details (e.g., extractables, leachables) may need to be submitted. However, in cases where interaction is unlikely, such as solid oral dosage forms, information may not be submitted.

5.P.8 Stability The results of stability studies conducted under accelerated and long-term storage conditions for at least 1 month for the batches representing the test product to be used in bioequivalence trials must be submitted. Nevertheless, before the bioequivalence trial commences, at least the initial data of stability studies conducted under accelerated and long-term storage conditions for the test product batch(es) to be used in the bioequivalence trial must be submitted, and it must be declared that the stability studies will continue in accordance with the protocol for the relevant batch(es). The results obtained from stability studies should be summarized in tabular form. Supporting data pertaining to stability studies carried out during drug development stages should be summarized in tabular form. An evaluation of the available data and a justification for the proposed shelf life of the test product should be submitted. Extrapolation may be performed provided that the stability studies are conducted in parallel with the bioequivalence trial.

6. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF PLACEBO PRODUCTS The requirements for placebo products to be used in the clinical trial are limited to the following sections.

6.P Placebo Products Used in the Clinical Trial

6.P.1 Description and Composition The complete qualitative and quantitative composition of the clinical trial product must be specified. The dosage form and the function of each excipient should be presented in tabular form with a brief description.

6.P.2 Pharmaceutical Development An explanation must be submitted regarding the resolution of possible differences between the investigational product and the placebo product in terms of taste, appearance, and odor.

6.P.3 Manufacture

6.P.3.1 Manufacturer(s) For placebo products to be used in the clinical trial, the name(s), address(es), and responsibilities of all manufacturers, including contractors, and each manufacturing site involved in the manufacturing, packaging/assembly, and testing stages must be specified. In cases where the placebo product is to be re-packaged or re-labeled at trial sites that do not hold a "manufacturing site license" for exclusive use in the trial, the relevant provision requirements of the Good Manufacturing Practices (GMP) Guide for Human Medicinal Product Manufacturing Facilities must be taken into consideration. It must be stated in this section that such activities will be carried out.

6.P.3.2 Batch Formula The batch formula and batch size of the batch to be used in the clinical trial must be submitted.

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6.P.3.3 Description of Manufacturing Process and Process Controls A flow diagram and a brief description of the manufacturing process should be submitted for consecutive manufacturing steps, indicating the components used at each manufacturing step and the relevant in-process controls. Non-standard manufacturing processes, novel technologies, or new packaging processes should be described in further detail.

6.P.3.4 Control of Critical Steps and Intermediates See Section 2.P.3.4.

6.P.3.5 Process Validation and/or Evaluation Not applicable for placebo products. However, in cases where non-standard sterilization procedures (not included in the Pharmacopoeia) are applied, the critical manufacturing steps, validation of the manufacturing process, and the process controls applied must be submitted.

6.P.4 Control of Excipients

6.P.4.1 Specifications References to the Pharmacopoeia must be specified. For mixtures of excipients composed of substances included in the Pharmacopoeia (e.g., premixed dry blend for film coating), it is sufficient to submit the general specifications for the mixture. For excipients not included in the Pharmacopoeia, an in-house monograph must be submitted. Specifications must be submitted for the capsule shell.

6.P.4.2 Analytical Procedures In cases where a reference to a Pharmacopoeia monograph cannot be made, the analytical methods used must be specified.

6.P.4.3 Validation of Analytical Procedures Not applicable.

6.P.4.4 Justification of Specifications Not applicable.

6.P.4.5 Excipients of Human or Animal Origin See Section 7.A.2

6.P.4.6 Novel Excipients For novel excipients, detailed information must be provided on the manufacturing process, characterization, and controls related to product safety. In accordance with the relevant clinical trial phase, the information specified in Section 3.2.S of the CTD should be submitted (see Section 7.A.3); for example, information on the manufacturing process, characterization, and stability should be included.

6.P.5 Control of the Placebo Product

6.P.5.1 Specifications The release and shelf-life specifications for the placebo product batches to be used in the clinical trial, the tests used, and their acceptance criteria must be specified. The specifications must include at least one test capable of clearly identifying the difference between the placebo and the investigational product.

6.P.5.2 Analytical Procedures Analytical methods must be specified for all tests included in the specifications of the finished product (e.g., dissolution test method). It is not necessary to provide detailed analytical procedures.

6.P.7 Container Closure System The primary packaging material to be used for the clinical trial product must be specified. Additionally, in cases where the secondary packaging material affects the quality of the finished product, the secondary packaging must also be specified.

6.P.8 Stability The storage conditions and shelf life of the placebo product must be specified. The shelf life of the placebo product should preferably cover the expected duration of the clinical trial. A stability study must be conducted in cases where changes may occur in the physical properties of the placebo product or where there is a possibility of degradation of the placebo product. In all other cases, a brief justification for the assigned shelf life will be sufficient.

7. APPENDICES TO THE INVESTIGATIONAL PRODUCT DOSSIER

7.A.1 Facilities and Equipment Not applicable.

7.A.2 Safety Evaluation of Adventitious Agents All human or animal-derived materials used in the manufacturing process of both the active substance and the finished product, or such materials that come into contact with the active substance or finished product throughout the manufacturing process, must be identified. Risk assessment information regarding potential contamination with adventitious agents of human or animal origin should be submitted in this section.

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TSE Agents Detailed information must be provided in accordance with international guidelines on the prevention and control of TSE (transmissible spongiform encephalopathy) agents. This information may include certification and control of the manufacturing process as appropriate to the material, process, and agent.

Viral Safety Where applicable, risk assessment information regarding potential viral contamination should be submitted in this section. The risk of viral contamination of the product and the capacity of the manufacturing process to remove or inactivate viruses should be evaluated.

Other Adventitious Agents Detailed information regarding other adventitious agents such as bacteria, mycoplasmas, and fungi should be submitted in the appropriate sections of the main dossier.

7.A.3 Novel Excipients In accordance with the relevant clinical trial phase, the information specified in Section 3.2.S of the CTD must be submitted for novel excipients.

7.A.4 Solvents Used for Reconstitution and Dilution Where applicable, the relevant information specified in Section 3.2.P of the CTD must be submitted for solvents used for reconstitution and dilution.

8. AUXILIARY MEDICINAL PRODUCTS For auxiliary medicinal products, the same requirements and principles applied to investigational products apply. For auxiliary medicinal products authorized by the competent authorities, a complete application must be submitted in accordance with the requirements specified in Sections 3 and 4 of this guideline.

9. SUBSTANTIAL MODIFICATIONS AND MODIFICATIONS MADE TO THE INVESTIGATIONAL PRODUCT DOSSIER In accordance with Good Manufacturing Practices (GMP), Product Specification Files must be maintained for each investigational product at the relevant site and must be continuously updated to ensure traceability throughout the product development process. Current Product Specification Files must also be maintained for auxiliary medicinal products to the extent applicable. After the trial authorization has been obtained, modifications may be permitted to be made to the trial. A modification may take the form of updating existing information and documents or adding new information and documents. Any modification to any aspect of the trial made subsequent to the trial authorization that may have a significant impact on the safety and rights of the participants and/or on the reliability and validity of the data to be obtained in the trial is defined as a substantial modification. Modifications that do not fall within the scope of substantial modifications are referred to as modifications. When evaluating the investigational product dossier, the focus should be on patient safety. Therefore, any modification involving a potential new risk must be considered a substantial modification. Substantial modifications particularly cover the impurity profile, microbial contamination, viral safety, situations related to TSE changes, and situations where toxic degradation products may form. In the event that the investigational product dossier is updated, a document indicating the modifications must be submitted to the ethics committee and the Agency, along with the new investigational product dossier updated with the date and, where applicable, version number. Furthermore, for updates made to the investigational product dossier, a table containing the current/proposed status of the modification, its justification, and the item number related to the modification specified in Annex-1 must also be attached to the application. The template table to be attached to the application is provided in Annex-2.

10. ENTRY INTO FORCE This guideline enters into force on the date of its publication. For bioequivalence trial applications, the requirement for the submission of the investigational product dossier will become effective as of 1 January 2025.

11. EXECUTION The President of the Agency executes the provisions of this guideline.

References 1. REGULATION ON CLINICAL TRIALS OF HUMAN MEDICINAL PRODUCTS published in the Official Gazette No. 32203 dated 27/05/2023 2. REGULATION ON MEDICAL DEVICE CLINICAL TRIALS published in the Official Gazette No. 31890 dated 08/07/2022 3. GOOD CLINICAL PRACTICE GUIDE 4. CTD GUIDE 5. GUIDELINE ON THE INVESTIGATION OF

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BIOAVAILABILITY AND BIOEQUIVALENCE OF HUMAN MEDICINAL PRODUCTS 6. GOOD MANUFACTURING PRACTICES (GMP) GUIDE FOR HUMAN MEDICINAL PRODUCT MANUFACTURING FACILITIES 7. ICH: IMPURITIES IN NEW DRUG SUBSTANCES Q3A(R2) 8. ICH: IMPURITIES IN NEW DRUG PRODUCTS Q3B(R2) 9. ICH: IMPURITIES: GUIDELINE FOR RESIDUAL SOLVENTS Q3C(R8) 10. ICH: GUIDELINE FOR ELEMENTAL IMPURITIES Q3D(R2) 11. ICH: VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1) 12. ICH: STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

13. ICH: SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES Q6A 14. ICH: GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS M3(R2) 15. ICH: ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK M7(R2) 16. REFLECTION PAPER ON THE QUALIFICATION OF NON-GENOTOXIC IMPURITIES (EMA/CHMP/SWP/545588/2017) 17. NOTE FOR GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICINAL PRODUCTS (EMA/410/01 Rev. 3) 18. ANNEX II TO NOTE FOR GUIDANCE ON PROCESS VALIDATION: NON-STANDARD PROCESSES (CPMP/QWP/2054/03) 19. GUIDELINE ON RADIOPHARMACEUTICALS (EMEA/CHMP/QWP/306970/2007)

RATIONALE FOR REVISION Revision No Revision Date Rationale and Explanations 01 The date determined for the submission of the investigational medicinal product dossier in bioequivalence study applications was updated.

ANNEXES ANNEX-1 CHANGES TO BE MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER CHANGES TO BE MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER Rationale Type of Change Substantial Change (1) Change (2) 1. Change in the Manufacturer(s) of the Active Substance 1.1.1. Addition of a new manufacturer or change of manufacturer (if it is a different company, or the same company but in a different country) 1.1.2. Removal of a manufacturing or testing site (for quality/safety reasons or due to non-compliance with GMP requirements) 1.2.1. Alternative manufacturing site of the same company (with the same manufacturing process and the same specifications) 1.2.2. Change only in the name and address of the active substance manufacturer (provided that the manufacturing site and all manufacturing operations remain the same) 1.2.3. Removal of a manufacturing or testing site (not arising from quality/safety reasons) 1.2.4. Addition or change of a testing site (provided that the same analytical methods are used and the analytical method transfer is carried out) 2. Change in the Manufacturing Process of the Active Substance 2.1.1. A different synthesis method 2.1.2. Broadening of the in-process acceptance criteria and process parameters in a manner affecting the quality and safety of the product 2.1.3. Change in the physicochemical properties affecting the quality of the investigational medicinal product (particle size distribution, polymorphism in solid dosage forms, etc.) 2.1.4. Change in the manufacturing process of the active substances of herbal medicinal products (herbal drug or herbal preparation) 2.2.1. Broadening of the in-process acceptance criteria and process parameters in a manner that does not affect the quality and safety of the product (minor changes in solvents, reagents, catalysts, temperature, pressure, reaction time or stoichiometry, having the same process and synthesis method, provided that they do not affect the impurity profile or physicochemical properties of the active substance) 2.2.2. Increase in batch size in a manner that does not affect the impurity profile or physicochemical properties 2.2.3. Change in the physicochemical properties in a manner that does not affect the quality of the investigational medicinal product (e.g., change in particle size distribution for drugs with high solubility, particle size distribution and/or polymorphism for drugs containing spray-dried dispersion) 2.2.4. Addition or intensification of in-process controls (not arising from safety reasons) 2.2.5. Repetition of a process included in the investigational medicinal product dossier (e.g., repetition of a purification step) 3. Change in the Specifications of the Active Substance 3.1.1. Broadening of acceptance criteria 3.1.2. Deletion of a specification parameter 3.2.1. Narrowing of

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acceptance criteria (not arising from safety reasons) 3.2.2. Addition of specification parameter(s) (not arising from safety reasons)

CHANGES TO BE MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER Rationale Type of Change Substantial Change (1) Change (2) 3.1.3. Addition of specification parameter(s) due to safety/quality reasons (e.g., addition of a control for mutagenic impurities)

3.2.3. Addition, deletion or modification of a specification parameter due to updates made in pharmacopoeial monographs 4. Change in the Test Methods of the Active Substance/Finished Product 4.1.1. A new or different test method (e.g., NIR instead of HPLC) or method changes requiring new validation (if the results obtained are not superior or equivalent to the approved method and/or affect the control strategy or specification) 4.2.1. Improvement of the same analytical method, provided that the following conditions are met (e.g., higher sensitivity, precision, accuracy) 1. If the acceptance criteria are the same or narrower, 2. If the improved method is suitable for use or validated in accordance with the development stage and provides comparable or superior validation results. 4.2.2. Updating of test procedures in order to ensure compliance with updates made in pharmacopoeial monographs 5. Reference Standard Change 5.2.1. Recognition of a new reference standard, provided that equivalence with the previous reference standard is ensured 6. Change in the Re-Test Period of the Active Substance 6.1.1. Shortening of the re-test period and/or restriction of the storage conditions due to safety/quality reasons 6.1.2. Extension of the re-test period without being based on an already approved stability protocol or without a prior commitment 6.1.3. Extension of the stability protocol duration by adding additional time points in order to extend the re-test period 6.2.1. Extension of the re-test period based on the already approved stability protocol or scheme 6.2.2. Shortening of the re-test period and/or modification of the storage conditions to be more restrictive (the reason for the change in question should not be unexpected events arising from the manufacturing process or stability) 6.2.3. Addition of intermediate points to the stability time points in order to intensify the intermediate analyses without modifying the extrapolation conditions (e.g., addition of a 42-month stability time point) 7. Change in the Formulation of the Investigational Medicinal Product 7.1.1. Change in the qualitative and quantitative composition of one or more excipients that may have a significant impact on the quality and safety of the investigational medicinal product (replacement of an excipient with another excipient having the same functional property, e.g., a disintegrant) 7.1.2. Change in and/or addition to the weight of the finished product 7.2.1. The non-functional coating material of the tablet having a composition that is qualitatively the same but quantitatively different, in a manner that will not have any effect on blinding 7.2.2. Change in the shapes of immediate-release tablets in cases where there is no effect on blinding and the dissolution profiles of the old shape and the new shape are comparable (e.g., converting the tablet from a round shape to an elliptical shape) 7.2.3. Change in imprinting/embossing/other markings, provided that there is no effect on blinding

CHANGES TO BE MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER Rationale Type of Change Substantial Change (1) Change (2) 8. Change in the Manufacturers of the Investigational Medicinal Product 8.1.1. Addition or change of a manufacturing/packaging/testing site 8.1.2. Removal of a manufacturing/packaging/testing site (for quality/safety reasons or due to non-compliance with GMP requirements) 8.1.3. Addition or change of a batch release site 8.2.1. Removal of a manufacturing, packaging or testing site (not arising from quality/safety reasons) 8.2.2. Change of the manufacturer name 8.2.3. Addition or change of an import site that is not a batch release site and holds a valid GMP certificate 9. Change in the Manufacturing Process of the Investigational Medicinal Product 9.1.1. Significant change in the manufacturing process (e.g., wet granulation versus direct compression, fluidized bed granulation versus conventional granulation) and in critical process controls (e.g., bioburden limit) 9.1.2. Increase in batch size in non-standard processes 9.1.3. Increase in batch size in standard manufacturing processes in such a way that the scale-up factor exceeds 10 9.2.1. Change in the process (same process) parameters in cases where an effect on the quality of the product is not expected 9.2.2. Increase in batch size in standard

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manufacturing processes in such a way that the scale-up factor does not exceed 10 10. Change in the Specifications of Excipients (That May Affect Product Performance) 10.1.1. Change in the particle size distribution affecting in vitro dissolution

11. Change in the Test Methods of Excipients Not Included in the Pharmacopoeia 11.1.1. A new or different test method (e.g., NIR instead of HPLC) 11.2.1. A minor change in a test method already included in the investigational medicinal product dossier 11.2.2. Update made in test procedures in order to ensure compliance with pharmacopoeial monographs 12. Change in the Specifications of the Investigational Medicinal Product (Release and Shelf-Life Specifications) 12.1.1. Broadening of the clinically relevant acceptance criteria (e.g., a hardness change affecting in vitro dissolution and/or disintegration time) or broadening of the acceptance criteria for impurities 12.1.2. Deletion of a specification parameter 12.1.3. Addition of specification parameter(s) due to safety/quality reasons or clinically relevant ones (e.g., control of polymorphs having the potential to change during the manufacturing and stability of the finished product, control of unqualified impurities, or control of mutagenic impurities) 12.2.1. Narrowing of acceptance criteria (not arising from safety reasons) 12.2.2. Addition of specification parameter(s) (not arising from safety reasons, except for the control of mutagenic impurities) 13. Change in the Container Closure System 13.1.1. New container closure system (e.g., less protective material, a different container/material for liquid products)

CHANGES TO BE MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER Rationale Type of Change Substantial Change (1) Change (2) 14. Change in Medical Devices 14.1.1. Addition/replacement/modification of a medical device having a potential impact on quality, safety and/or efficacy 14.2.1. Addition/replacement/modification of a medical device considered to have no impact on quality, safety and/or efficacy 15. Change in the Stability of the Investigational Medicinal Product 15.1.1. Reduction of the shelf life and/or restriction of the storage conditions due to safety and/or quality reasons 15.1.2. Extension of the shelf life without being based on an already approved stability protocol or without a prior commitment 15.1.3. Extension of the stability protocol duration by adding additional time points in order to extend the shelf life 15.2.1. Extension of the shelf life based on the already approved stability protocol or scheme 15.2.2. Addition of intermediate points to the stability time points in order to intensify the intermediate analyses without modifying the extrapolation conditions (e.g., addition of a 42-month stability time point)

ANNEX-2 CURRENT-PROPOSED JUSTIFICATION TABLE FOR CHANGES Requested Change Current Status Proposed Status Justification for Change Corresponding Article Number in Annex-1 for the Relevant Change

ANNEX-3 DECISION TREE

HUMAN MEDICINAL PRODUCTS USED IN CLINICAL TRIALS INVESTIGATIONAL PRODUCTS INVESTIGATIONAL PRODUCTS (TEST/COMPARATOR/PLACEBO) FOR PHASE I, II AND III CLINICAL TRIALS INVESTIGATIONAL PRODUCTS NOT AUTHORIZED BY COMPETENT AUTHORITIES SECTION 2 INVESTIGATIONAL PRODUCTS AUTHORIZED BY COMPETENT AUTHORITIES UNMODIFIED AUTHORIZED INVESTIGATIONAL PRODUCTS SECTION 3 MODIFIED AUTHORIZED INVESTIGATIONAL PRODUCTS SECTION 4 PLACEBO SECTION 6 INVESTIGATIONAL PRODUCTS FOR BIOEQUIVALENCE (BE) STUDIES REFERENCE PRODUCT REFERENCE PRODUCTS AUTHORIZED BY COMPETENT AUTHORITIES UNMODIFIED AUTHORIZED REFERENCE PRODUCT SECTION 3 MODIFIED AUTHORIZED REFERENCE PRODUCT SECTION 4 REFERENCE PRODUCTS NOT AUTHORIZED BY COMPETENT AUTHORITIES SECTION 2 TEST PRODUCT SECTION 5 AUXILIARY HUMAN MEDICINAL PRODUCTS UNMODIFIED AUTHORIZED AUXILIARY HUMAN MEDICINAL PRODUCTS SECTION 3 MODIFIED AUTHORIZED AUXILIARY HUMAN MEDICINAL PRODUCTS SECTION 4

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