GUIDELINE ON QUALITY REQUIREMENTS FOR BIOLOGICAL MEDICINAL PRODUCTS USED IN CLINICAL TRIALS KAD-KLVZ-28 (22 January 2024) Rev.00

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ANNEXES

ANNEX-1 CHANGES MADE IN THE INVESTIGATIONAL PRODUCT DOSSIER

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1. INTRODUCTION 1.1. Purpose and Legal Basis The purpose of this guideline is to establish the quality requirements for biological/biotechnological human medicinal products to be used in clinical trials to be conducted in Turkey, taking into account national and international standards. This Guideline has been prepared taking into consideration the Regulation on Clinical Trials of Human Medicinal Products published in the Official Gazette No. 32203 dated 27/05/2023 and, within the framework of alignment with European Union legislation, the Guideline on the requirements for quality documentation concerning biological investigational medicinal products in clinical trials (EMA/CHMP/BWP/534898/2008). In clinical trial applications involving biological/biotechnological human medicinal products, the requirements concerning the quality of these products shall be in accordance with the principles outlined in international guidelines and shall be taken into account throughout the product development process. In addition, the Guidelines on Virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) and the Strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07) guidelines shall also be taken into consideration. However, since different clinical trials and investigational products may be involved, it is not possible to define in detail requirements that would be applicable to all different situations. Nevertheless, this guideline contains explanations regarding the general information to be presented in the quality section of the investigational product dossier. The Agency and the relevant ethics committee may request additional information and documentation where necessary. In all phases of clinical trials, it is the responsibility of the applicant to ensure the protection of participants by using an investigational product fit for purpose and of high quality, and to appropriately address quality characteristics that may pose a risk to participant safety (e.g., microbiological aspects, viral contamination, dose). 1.2. Scope This guideline addresses the dossier requirements concerning the biological, chemical and pharmaceutical quality of investigational products containing biological/biotechnological active substances. This guideline covers proteins and polypeptides, their derivatives, and products of which they are components (e.g., conjugates). These proteins and polypeptides are produced from recombinant or non-recombinant cell culture expression systems and can be highly purified and characterised using an appropriate set of analytical procedures. The guideline also covers auxiliary human medicinal products containing these proteins and polypeptides as active substances. The requirements for auxiliary human medicinal products vary depending on whether the product in question is a modified authorised or unmodified authorised human medicinal product. This guideline may also be applicable to other product types, such as proteins and polypeptides isolated from tissues and body fluids. Furthermore, this guideline also lists examples of changes to the biological, chemical and pharmaceutical quality requirements of the investigational product. Advanced therapy medicinal products are outside the scope of this guideline.

When preparing the investigational medicinal product dossier for phase II and phase III clinical trials, it should be taken into account that a larger number of volunteers will be exposed to the investigational medicinal product and that the duration of exposure will be longer compared to phase I clinical trials. 1.3. General Considerations for All Investigational Medicinal Products All investigational medicinal products shall be manufactured in compliance with the requirements of the Guide to Good Manufacturing Practice (GMP) for Manufacturers of Human Medicinal Products. 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 that the investigational medicinal product dossier contains the most up-to-date information available on the clinical trial as of the date of submission of the application. Where the active substance used has already been authorised by the competent authorities in a human medicinal product, reference may be made to that authorisation, provided it remains valid. In this

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case, the marketing authorisation holder or the active substance manufacturer shall submit a written 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 human medicinal product. In addition, the name of the human medicinal product, the authorisation number, the marketing authorisation holder and the country that granted the authorisation shall be specified. Depending on the structure of the product, additional information may be requested. 1.5. Definitions Analytical procedure: All steps followed in performing the analysis (a detailed description of the equipment and consumables to be used; the preparation of samples, reference standards and other reagents; calculation formulae, etc.), Analytical method: The underlying principle of the method used to perform the analysis (e.g. GC-MS), Investigational medicinal product: A human medicinal product that is tested or used as a reference in a clinical trial, including placebo, Investigational Medicinal Product Dossier (IMPD): The document containing information on the quality, manufacture and control of the investigational medicinal product, together with 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 (adaptation of the European Pharmacopoeia), 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 considered appropriate by the Agency, Agency: TİTCK (Turkish Medicines and Medical Devices Agency),

Modified Authorised Investigational Medicinal Product: A human medicinal product authorised by the competent authorities in which changes have been made to the particulars forming the basis of the authorisation, Unmodified Authorised Investigational Medicinal Product: A human medicinal product authorised by the competent authorities in which no changes have been made to the particulars forming the basis of the authorisation, Common Technical Document (CTD): The internationally agreed format for the orderly presentation of applications to be submitted to the regulatory authorities of the three ICH regions, namely Europe, the United States and Japan, Competent Authority: Together with TİTCK (Turkish Medicines and Medical Devices Agency), the ICH (International Council for Harmonisation) founding member competent authorities (the United States Food and Drug Administration (US FDA), the European Medicines Agency (EMA), and the Pharmaceuticals and Medical Devices Agency of Japan (PMDA)), or the standing member competent authorities (the Swiss national medicines authority (Swissmedic) and the Canadian national medicines authority (Health Canada)), the Australian national medicines authority (TGA) or the national medicines authority of the United Kingdom (MHRA), shall mean. 2. INFORMATION ON THE BIOLOGICAL, CHEMICAL AND PHARMACEUTICAL QUALITY OF BIOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS 2.S Active Substance For biological/biotechnological active substances, reference to an Active Substance Master File (ASMF) or a Certificate of Suitability to the European Pharmacopoeia (CEP) is not accepted and is not considered valid. 2.S.1 General Information 2.S.1.1 Nomenclature Information on the nomenclature of the active substance (e.g. INN name, pharmacopoeial name, trademark name, company code and, if available, other names or codes) shall be provided. 2.S.1.2 Structure A brief description of the expected structure shall be provided. Where possible, the higher-order structure, a schematic amino acid sequence indicating the glycosylation sites or other post-translational modifications, and the relative molecular mass shall be provided. 2.S.1.3 General Properties A list of the physicochemical and other relevant properties of the active substance, including biological activity (the specific ability or capacity of a product to achieve a defined biological effect), shall be provided. 2.S.2 Manufacture 2.S.2.1 Manufacturer(s) The name, address and responsibilities of each manufacturer, including contractors, and of each manufacturing site or facility responsible for production, testing and batch release shall be specified. 2.S.2.2 Description of the Manufacturing

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Process and Process Controls The manufacturing process and process controls shall be described adequately. The manufacturing process typically starts with one or more cell bank vials and includes cell culture, harvest(s), purification, modification reactions and filling steps. Storage and transport conditions shall be outlined. A flow chart shall be provided for all consecutive steps, including relevant process parameters and in-process tests. The process control strategy should focus on safety-related in-process controls, and acceptance criteria shall be established for critical steps in the manufacture of phase I/II material (e.g. ranges of process parameters for steps involved in virus removal). These in-process controls (process parameters and in-process tests as defined in ICH Q11) shall be presented together with action limits or provisional acceptance criteria. For other in-process controls, monitoring is sufficient; there is no need to present acceptance criteria or

action limits. Since the control limits in early phase trials are based on a limited number of development batches, these limits are provisional in nature. As additional information on the process is acquired throughout the stages of drug development, more detailed information on the in-process controls shall be provided and the acceptance criteria shall be reviewed. The batch(es) and batch size shall be defined, including information on the pooling of harvests or intermediates. Any instances where a process is repeated during the manufacture of the active substance (e.g. filter integrity test failure) shall be indicated and justified. Repetition of a process may be carried out in exceptional circumstances. For biological/biotechnological products, these exceptional circumstances are generally limited to specific re-filtration and re-concentration steps for reasons such as technical failure of equipment or mechanical failure of the chromatography column. 2.S.2.3 Control of Materials Raw materials and starting materials The materials used in the manufacture of the active substance (raw materials, starting materials, cell culture media, growth factors, column resins, solvents, reagents, etc.) shall be listed, indicating where each material is used in the process. Reference shall be made to quality standards (pharmacopoeial monographs or manufacturers' in-house specifications). Where a non-standard (not included in a pharmacopoeia) material is used, information on the quality and control of such material shall be provided. Information demonstrating that the materials (including biological-source materials such as media components, monoclonal antibodies and enzymes) meet applicable standards for their intended uses shall be provided. For all raw materials of human or animal origin (including those used in the preparation of cell banks), the source of the material and the relevant stage of the manufacturing process in which it is used shall be specified. For these materials, a summary of safety information relating to adventitious agents shall be provided in Annex A.2. Source, history and generation of the cell substrate Information on the source and generation of the cell substrate (a flow chart for consecutive manufacturing steps), the analysis of the expression vector incorporated into the parental/host cell used for genetic modification of the cells and used to develop the Master Cell Bank (MCB), and the strategy for inducing and controlling the expression of the relevant gene in production shall be provided in accordance with the principles of the ICH Q5D Guideline. Cell bank system, characterisation and testing The Master Cell Bank (MCB) shall be established before the start of phase I clinical trials. A Working Cell Bank (WCB) cannot always be established. Information on the preparation, qualification and storage of the cell banks shall be provided. If used, the Master Cell Bank and/or the Working Cell Bank shall be characterised and the results of the tests performed shall be provided. For mammalian cell lines, the clonality of the cell banks shall be addressed. The preparation and characterisation of the cell banks shall be carried out in accordance with the principles of the ICH Q5D Guideline. In order to ensure the identity, viability and purity of the cells used for production, the cell banks shall be characterised in terms of relevant phenotypic and genotypic markers.

Prior to the initiation of clinical trials, the nucleic acid sequence of the expression cassette, including the sequence of the coding region, should be verified. As with any process change, the implementation of a working cell bank may potentially affect the quality profile of the active substance, and therefore comparability should be considered (see section 2.S.2.6 Manufacturing

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process development). The safety evaluation regarding unexpected agents and the qualification of cell banks used for the manufacture of the active substance should be presented in Annex A.2. Stability of the cell substrate All available data on the stability of the cell substrate should be presented. 2.S.2.4 Control of Critical Steps and Intermediates The tests performed and acceptance criteria for the control of critical steps in the manufacturing process should be specified. Reference may be made to section 2.S.2.2 for acceptance criteria or action limits. It is acknowledged that, due to the limited data available in early phase studies (Phase I/II) during the drug development process, all of this information may not be available. Hold times and storage conditions for intermediates should be supported and justified by relevant data. 2.S.2.5 Process Validation and/or Evaluation Not applicable to active substances to be used in clinical trials. Relevant information on manufacturing steps for the removal or inactivation of viral contaminants should be presented in Annex A.2. 2.S.2.6. Manufacturing Process Development Process improvement Manufacturing processes and process control strategies are continuously improved and optimized, particularly during the development stage and the initial phases of clinical trials. Changes in the manufacturing process and process controls should be summarized. In order to establish an appropriate link between pre-change and post-change batches, this description should ensure the clear identification of the versions of the manufacturing process used in the production of each batch used in nonclinical and clinical trials. Comparative flow charts and/or a list of process changes may be used to present process development. If a process change has been made in steps related to viral clearance, a justification should be provided as to whether a new viral clearance study is required or whether the previous study remains valid. Comparability study Depending on the results of the change made and the stage of drug development, a comparability study may be required in order to demonstrate that the change will not adversely affect the quality of the active substance. In the early phases of a clinical trial, the primary purpose of this application is to provide assurance that the post-change product is suitable for future clinical trials and will not raise any concern regarding the safety of volunteers enrolled in the clinical trial. Furthermore, for subsequent phases of the clinical trial, it should be evaluated whether the post-change material will affect the efficacy of the investigational product.

The comparability study should normally follow a stepwise approach involving a comparison of the quality characteristics of the active substance and relevant intermediates using appropriate analytical methods. Analytical methods generally include routine tests and may be supported, as appropriate, by additional characterization tests (including orthogonal methods). In cases where the manufacturers' relevant knowledge and experience are insufficient to evaluate the risk introduced by the change, or where a potential risk to volunteers is anticipated, a comparability study based solely on quality considerations may not be sufficient. Comparability testing in nonclinical and early phases of clinical trials may not be comprehensive. In the case of Phase I clinical trials, an investigational product that is representative of the material used in nonclinical studies should be used (see Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07)). 2.S.3 Characterization 2.S.3.1 Elucidation of Structure and Other Properties To ensure that an appropriate specification is established, characterization of a biotechnological or biological active substance with appropriate techniques (including the determination of physicochemical properties, biological activity, immunochemical properties, purity, and impurities) is required. For modifications of no safety concern (e.g., C-terminal lysine for monoclonal antibodies), reference to literature data alone is not acceptable unless otherwise justified by prior knowledge obtained from similar molecules. Adequate characterization should be performed during the development stage preceding Phase I clinical trials and, where necessary, following significant process changes. All available information on primary, secondary, and higher-order structure, including post-translational modifications (e.g., glycoforms) and other modifications of the active substance, should be presented. Details regarding biological activity should be presented. Generally, prior to the initiation of Phase I clinical trials, the biological activity should be determined using a suitable,

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reliable, and qualified method. If such a method is not available, this matter should be justified. It is acknowledged that the extent of characterization data will increase throughout the drug development stages. A rationale for the selection of the methods used in characterization should be provided, and the suitability of these methods should be justified. 2.S.3.2 Impurities Process-related impurities (e.g., host cell proteins, host cell DNA, media residuals, column leachables) and product-related impurities (e.g., precursors, cleaved forms, degradation products, aggregates) should be specified. Quantitative information on impurities, including the maximum amount of the highest clinical dose, should be presented. An estimate of clearance may be justified for certain process-related impurities (e.g., antifoam agents) in the finalized process. If only qualitative data are presented for certain impurities, this should be justified. 2.S.4 Control of the Active Substance In the absence of process validation data, the quality characteristics used to control the active substance are important in terms of demonstrating pharmaceutical quality, product consistency, and comparability after process changes. Therefore, the quality characteristics controlled throughout the drug development process should not be limited to the tests included in the specification for which provisional acceptance criteria have been established.

2.S.4.1 Specifications The specifications for active substance batches used in the clinical trial, the tests used, and their acceptance criteria should be specified. Identity, purity, and assay tests are mandatory, and limits in the form of 'record' or 'report results' for these quality characteristics are not acceptable. Unless otherwise justified, a test for biological activity should be included in the specifications. Upper limits should be established for impurities, taking safety considerations into account. The microbiological quality of the active substance should be specified in the specifications. Since acceptance criteria are based on a limited number of nonclinical and clinical batches, they are provisional in nature, and these acceptance criteria may need to be reviewed and re-established during subsequent drug development stages. Product characteristics that have not been precisely determined at a given drug development stage (e.g., glycosylation, charge heterogeneity) or product characteristics for which available data are too limited to establish relevant acceptance criteria should also be recorded. Such product characteristics may be included in the specification without pre-defined acceptance limits. In such cases, limits in the form of 'record' or 'report results' may be acceptable. Results should be presented in the batch analysis section (2.S.4.4). Additional information for Phase III clinical trials As knowledge and experience increase, it may be necessary to add or remove specifications and to modify analytical methods. The specifications and acceptance criteria established during the drug development stages should be reviewed and re-established. 2.S.4.2 Analytical Procedures The analytical methods (chromatographic methods, bioassays, etc.) used for all tests included in the specifications of the active substance, including tests reported without acceptance limits, should be listed. A brief description should be provided for all non-compendial (not included in a pharmacopoeia) analytical procedures, highlighting the controls used in the analysis. For methods consistent with a pharmacopoeial monograph, reference to these monographs will be sufficient. 2.S.4.3 Validation of Analytical Procedures Validation of analytical procedures is regarded as an evolving process throughout the drug development process. Analytical procedures included in a pharmacopoeia or for which reference is made to a product-specific pharmacopoeial monograph are considered validated. However, if modifications are made to the methods specified in pharmacopoeial monographs or if alternative methods are used, these methods should be validated. Information for Phase I and Phase II 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, assay and detection limit) and acceptance limits should be presented in tabular format. If analytical method validation studies have been performed during early phase studies, a summary table containing the results of these studies may be presented.

Information for Phase III Clinical Trials Validation of the analytical methods used for batch release and stability testing should be performed. It is sufficient to present the results of analytical method validation (e.g. the results or values found for specificity/selectivity, linearity, working

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range, accuracy, precision and, where required, assay and detection limit) in the form of a summary table. By the end of the Phase III clinical trial, full method validation, including the potency parameter, should have been completed. Submission of a full validation report is not required. 2.S.4.4 Batch Analyses Since the specifications may initially be very broad, actual batch data are important for quality assessment. Actual numerical values should be provided for quantitative parameters. The focus of this section is to demonstrate the quality of the batches to be used in the clinical trial (compliance with the preliminary specifications established). Since only a limited number of active substance batches are produced in the early clinical trial phases, test results obtained from the relevant non-clinical and clinical batches, including those to be used in the clinical trial applied for, should be submitted. For active substances with a longer manufacturing history, provided that it is justified, submission of results for only a few representative batches may be acceptable. The batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria and test results should be listed. The manufacturing process used for each batch and the differences between these processes should be indicated. A statement should be provided as to whether the batches for which analytical results are presented are among the batches to be used in the clinical trial, or whether additional batches not yet manufactured at the date of submission of the application will be used. 2.S.4.5 Justification of Specifications A justification should be provided for the quality attributes included in the specifications and the acceptance criteria established for purity, impurities, biological activity and other quality attributes that may be relevant to the performance of the medicinal product. Such justifications should be based on the relevant pharmaceutical development data and on the data obtained from stability studies, taking into account the batches used in non-clinical and/or clinical trials and the methods used for their control. It is acknowledged that acceptance criteria may be broader throughout the pharmaceutical development process. However, limits for quality attributes that could affect the safety of volunteers should be carefully evaluated in light of the available information (process capability, product type, dose, dosing duration, etc.). The suitability of the selected potency assay and the proposed acceptance limits should be justified. Where previously established specifications are modified (addition or removal of specification parameters, widening of acceptance criteria, etc.), these changes should be described and justified. 2.S.5 Reference Standards or Materials For biological/biotechnological active substances, a well-characterised reference material is inherently necessary to ensure consistency between different batches and, at the same time, to ensure comparability between the product to be placed on the market and the product used in clinical trials, and to establish a link between process development and commercial manufacturing. Characterisation of the reference material should be performed with accurate and reliable high-level analytical methods, and these analytical methods should be adequately described. Information on the manufacturing process used to establish the reference material should be submitted.

If more than one reference standard has been used during the pharmaceutical development process, a qualification history explaining how the relationship between the different standards has been maintained should be submitted. Where a pharmacopoeial standard exists, the pharmacopoeial standard should be used as the primary reference material. All in-house working standards should be qualified against this primary reference material. However, it should be taken into account that the use of a pharmacopoeial standard may be limited to certain test methods such as biological activity. Where no pharmacopoeial standard exists, an in-house standard should be established as the primary reference material during the pharmaceutical development process. The stability of the reference material should be monitored. This may be addressed within the company's quality system. 2.S.6 Container Closure System The primary packaging material used for the active substance should be stated. Possible interactions between the active substance and the primary packaging should be taken into consideration. 2.S.7 Stability Stability Summary and Conclusions (Protocol/Material and Methods) A stability protocol covering the proposed storage period of the active substance and, at the same time, including the specifications, analytical

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methods and testing intervals should be submitted. Testing intervals should normally be in accordance with the ICH Q5C Guideline. The quality of the active substance batches included in the stability programme should represent the quality of the product to be used in the relevant clinical trial. The active substance included in the stability programme should be stored in a container closure system of the same type and made of the same material as the active substance batches to be used in the clinical trial. Reduced-size containers are generally acceptable for stability testing of the active substance. Stability studies should evaluate the stability of the active substance under the proposed storage conditions. Accelerated stability and stress studies are recommended as they may help to understand the degradation profile of the product and may support extension of the shelf life. The methods used to analyse the stability-indicating attributes of the active substance should be discussed or cross-referenced to S.4.3 in order to guarantee that changes in the purity/impurity profile and potency of the active substance will be detected. Unless otherwise justified, the stability protocol should include a potency assay. A re-test period (as defined in the ICH Q1A Guideline) is not applicable to biological/biotechnological active substances. Stability Data and Conclusions Stability data should be submitted for at least one batch manufactured by a process representative of the manufacturing process used to produce the material to be used in the clinical trial. In addition, if available, supportive stability data on pharmaceutical development batches or batches manufactured using the previous manufacturing process should also be submitted. Provided that an appropriate justification for the representativeness of the quality of the clinical trial material is submitted, data from such batches may be used in determining the shelf life of the active substance. The relevant stability data should be presented in tabular format indicating the batches tested, the date of manufacture, the process version, the composition, the storage conditions, the time points, the test methods, the acceptance criteria and their results.

Actual numerical values should be provided for quantitative parameters. Any trend observed should be discussed. Available data and requirements regarding the stability of the active substance during the different phases of the clinical trial may be limited. Therefore, requirements may differ. By the time of Phase III, the applicant should have comprehensive knowledge of the stability profile of the active substance. Determination of Shelf Life The proposed shelf life of the active substance under the stated storage conditions should be specified and presented together with an assessment of the available data. Observed trends should be discussed. As stated in the ICH Q5C Guideline, the requested shelf life should be based on long-term, real-time and real-temperature stability studies. However, extension of the shelf life beyond the period covered by the real-time stability data may be acceptable where it is supported by accelerated stability studies and/or stability data obtained from representative material. The maximum shelf life after extension should not be more than twice the period covered by the real-time stability data obtained from the representative batch(es) or more than twelve months. However, extension of the shelf life beyond the planned duration of the long-term stability studies is not acceptable. Where an extension of the shelf life is planned, the applicant should undertake that it will be carried out in accordance with the protocol presented in the stability programme and that, in the event of unexpected problems arising, it will inform the Agency and the relevant ethics committee about such problems and the corrective actions related thereto. 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 should be stated. The information presented should include the following: - a brief description or table of the dosage form, - the composition, i.e. a list of all components of the dosage form and their amounts on a per unit basis (including overages, if any), the function of the components and reference to quality standards (pharmacopoeial monographs or the manufacturer's specifications), - a description of the accompanying diluent(s), - an outline of the container closure system used for the dosage form and, where applicable, the accompanying reconstitution diluents and devices. A full description should be presented in section P.7. 2.P.2 Pharmaceutical Development In the early stages of drug development, the information to be included in this section may be limited. A brief description of the formulation

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development should be provided, including the justification of any new pharmaceutical form or excipient. For investigational products requiring additional preparation such as reconstitution, dilution or mixing, the compatibility of the investigational product with the solvents, diluents and matrix used should be demonstrated. The method of preparation should be summarised and reference should be made to the full instructions included in the trial protocol or to the relevant instructions for use to be available at the trial site.

It must be demonstrated that the combination of formulation and packaging materials does not compromise the accuracy of dosing (for example, ensuring that the product is not adsorbed onto the wall of the container or the infusion system). This applies in particular to products with low doses and high dilution ratios. Where applicable, the safe administration of very small doses in first-in-human trials must be addressed as described in the Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products (EMEA/CHMP/SWP/28367/07).

Manufacturing Process Development All changes made to the manufacturing process, including changes in formulation and dosage form compared to previous clinical trials, must be described. Significant changes, such as formulation changes, must be supported by an appropriate comparability study. The data expected to be presented in this context are similar to those set out in section 2.S.2.6. These data must be sufficiently detailed to allow an accurate understanding of the changes and an assessment of their potential implications for volunteer safety. All changes made to the formulation during the phases of the clinical trial must be specified and justified with respect to their effects on the quality, safety, clinical characteristics, dose and stability of the finished product.

2.P.3 Manufacture 2.P.3.1 Manufacturer(s) The name(s), address(es) and responsibilities of all manufacturers, including contractors, and of each manufacturing site responsible for production, testing and batch release must be specified. Where more than one manufacturer is involved in the manufacture of the investigational product, the respective responsibilities must be clearly stated. In cases where the investigational product is to be re-packaged or re-labelled at trial sites that do not hold a "manufacturing site licence" for exclusive use in the trial, the relevant provision requirements of the Guide to Good Manufacturing Practices (GMP) for Manufacturers of Human Medicinal Products must be taken into consideration. The fact that these activities will be carried out must be stated in this section.

2.P.3.2 Batch Formula The batch formula and batch size of the batches to be used in the clinical trial must be presented.

2.P.3.3 Description of Manufacturing Process and Process Controls A flow diagram and a brief description of the manufacturing process must be provided for consecutive manufacturing steps, also indicating the components used at each manufacturing step and the relevant in-process controls. In-process controls may be recorded as action limits or reported as provisional acceptance criteria, and the focus should be placed on safety-related attributes. For other in-process controls, monitoring is sufficient; there is no need to present acceptance criteria or action limits. As additional information on the process is acquired throughout pharmaceutical development, more detailed information on in-process controls must be presented and acceptance criteria must be reviewed.

Most products containing recombinant proteins and monoclonal antibodies are manufactured by a non-standard aseptic process. Non-standard manufacturing processes or novel technologies and new packaging processes must be described in sufficient detail (see, for more detailed information, the Guideline on process

validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012)). The repetition of certain steps in the manufacturing process (e.g. re-filtration) may be acceptable, provided that these manufacturing steps are sufficiently defined and appropriately justified.

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2.P.3.4 Controls of Critical Steps and Intermediates The tests performed for the control of critical steps in the manufacturing process and the acceptance criteria must be specified. It is acknowledged that, due to the limited data available in early phase studies (Phase I/II) during pharmaceutical development, not all of this information may be available. Where a holding time is foreseen for intermediates, the duration and storage conditions must be specified and justified with data in terms of physicochemical, biological and microbiological attributes. For sterilising filtration, the maximum acceptable bioburden prior to filtration must be specified. It is commonly accepted as not more than '10 CFU/100 ml'. Where justified, a volume lower than 100 ml may be tested.

2.P.3.5 Process Validation and/or Evaluation Where applicable, the validation status of the aseptic process and lyophilisation must be briefly described. Taking into account the Guide to Good Manufacturing Practices (GMP) for Manufacturers of Human Medicinal Products, the validation of sterilisation processes must be of the same standard as that for licensed products. Information directly related to product safety, such as bioburden and media fill operations, must be specifically included in the file.

2.P.4 Control of Excipients 2.P.4.1 Specifications Reference may be made to the pharmacopoeia. For excipients not included in the pharmacopoeia, in-house specifications must be presented.

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

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

2.P.4.4 Justification of Specifications In-house specifications for excipients not included in the pharmacopoeia must be justified.

2.P.4.5 Excipients of Human or Animal Origin For excipients of human or animal origin, information on the safety evaluation of adventitious agents (e.g. sources, specifications, description of the tests performed) and on viral safety data must be prepared in accordance with the Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05) and presented in Annex A.2. In addition, compliance with the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01) must be documented in Annex A.2. Where human albumin or another plasma-derived medicinal product is used as an excipient, information on the safety evaluation of adventitious agents must follow the relevant sections of the Guideline on plasma-derived medicinal products (CPMP/BWP/706271/2010). If the plasma-derived

component has already been used in a human medicinal product authorised by the competent authorities, reference may be made to that product.

2.P.4.6 Novel Excipients For excipients used for the first time in a human medicinal product or used for the first time via a new route of administration, all detailed information on manufacture, characterisation and controls must be presented in the 2.S format, with reference to supporting safety data (nonclinical and/or clinical). For detailed information, see Annex A.3.

2.P.5 Control of the Clinical Trial Product 2.P.5.1 Specifications The same principles described for the establishment of the active substance specification must also be applied to the finished product. The release and shelf-life specifications of the batches of the investigational product to be used in the clinical trial, the tests used and their acceptance criteria must be specified. Identity, content and purity tests are mandatory. For sterile products, sterility and endotoxin tests are mandatory. Unless otherwise justified, a test for biological activity must be included in the specifications. Safety information must be taken into account when setting upper limits for impurities. During the stages of pharmaceutical development, the established specifications and acceptance criteria may need to be reviewed and rearranged. When establishing acceptance criteria for the quality attributes of the investigational product, safety considerations and the phase of the trial must be taken into account. As the acceptance criteria are based on a

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limited number of development, nonclinical and clinical batches, they are of a preliminary nature. They may need to be reviewed and rearranged during subsequent development stages. Analytical methods, content and bioactivity limits must ensure the accuracy of dosing. Safety information must be taken into account when setting upper limits for impurities not included in the active substance specifications.

Additional Information for Phase III Clinical Trials As information and experience regarding the investigational product increase, the need may arise to make changes to specification parameters or analytical methods. The specifications and acceptance criteria established during Phase I and Phase II clinical trials may need to be reviewed and rearranged.

2.P.5.2 Analytical Procedures Analytical methods must be specified for all tests included in the specifications of the finished product. For certain proteins and complex or innovative pharmaceutical forms, more advanced information may be required. For other requirements, see section 2.S.4.2.

2.P.5.3 Validation of Analytical Procedures For requirements, see section 2.S.4.3.

2.P.5.4 Batch Analysis As the specifications may initially be very broad, data from actual batches are important for the quality assessment. For quantitative parameters, actual numerical values must be presented. The focus of this section is to demonstrate the quality (compliance with the established specifications) of the batches to be used in the clinical trial. In early-phase clinical trials where only a limited number of batches have been manufactured

for trials, test results obtained from the relevant clinical and non-clinical batches, including those to be used in the clinical trial, should be submitted. For products with a longer manufacturing history, submission of results for only a few representative batches may be acceptable, provided that this is appropriately justified. Batch number, batch size, manufacturing site, date of manufacture, control methods, acceptance criteria, and test results should be listed. The manufacturing process used for each batch should be specified. A statement should be submitted indicating whether the batches for which analytical results are presented are the batches to be used in the clinical trial, or whether additional batches that have not yet been manufactured at the date of submission of the application will be used. 2.P.5.5 Characterisation of Impurities Additional impurities/degradation products observed in the investigational medicinal product but not covered under Section 2.S.3.2 should be specified and quantitatively measured. 2.P.6 Justification of Specifications The quality attributes included in the finished product specification should be justified primarily on the basis of the active substance specifications. Stability-indicating quality attributes should be taken into consideration. The proposed acceptance criteria should be justified. 2.P.7 Container Closure System The primary packaging material to be used for the investigational medicinal product should be specified. Where available, reference to the pharmacopoeial monograph may be made. If the investigational medicinal product is packaged in an administration device not included in the pharmacopoeia (non-standard), or if packaging materials not included in the pharmacopoeia (non-standard) are used, the packaging description and specifications should be provided. Where a medical device is to be used for the administration of the investigational medicinal product, its legal status should be clearly specified (e.g., whether it bears a CE mark for the intended use). In the absence of a certificate for the intended use, a declaration must be submitted confirming that the medical device complies with the relevant legal requirements regarding safety and performance requirements. In cases where a medicinal product is integrally combined with a medical device and the principal intended action is attributable to the medicinal product, this integral product is subject to pharmaceutical legislation and a CE mark is not required during development. However, in the application for marketing authorisation of the medicinal product, the requirements of paragraph 2 of Article 3 of Section I 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. For dosage forms with a high potential for interaction between the product and the container closure system (e.g., parenterals, ophthalmic products, oral solutions), additional detail (e.g., extractables, leachables) may need to be submitted within

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the scope of phase III clinical trials. 2.P.8 Stability The same requirements established for the active substance shall also apply to the finished product with respect to the stability protocol, stability results, extension of the shelf life

beyond the period covered by real-time stability data, stability commitment, and determination of shelf life including post-approval shelf life extension. Stability studies should guarantee that the investigational medicinal product will remain stable throughout the intended storage period. The data submitted should validate the proposed shelf life of the product from its release until its administration to volunteers. The stability protocol for the investigational medicinal product should take into account the information obtained about the stability profile of the active substance. Reduced designs, including bracketing and matrixing, may be acceptable if justified. Applicable stability data should be submitted for investigational medicinal products administered after reconstitution, dilution, or mixing, and for investigational medicinal products containing multiple doses. This study is not required if the investigational medicinal product is to be used immediately after opening or reconstitution. Information for Phase I Clinical Trials For phase I clinical trials, 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 should be submitted before the trial commences, and it should 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 batch(es) should be summarised in tabular format. An evaluation of the available data and a justification for the proposed shelf life of the investigational medicinal product should be submitted. Additional Information for Phase II and Phase III Clinical Trials Available stability data should be presented in tabular format. 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 should be submitted. The data should include results obtained from studies under long-term and, where available, accelerated storage conditions. INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER APPENDICES A.1 Facilities and Equipment Not applicable. 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, should be described. Risk assessment information regarding potential contamination with adventitious agents of human or animal origin should be submitted in this section. TSE Agents Detailed information should 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 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 documentation should comply with the requirements specified in the Guideline on virus safety evaluation of biotechnological investigational medicinal products (EMEA/CHMP/BWP/398498/05).

Other Adventitious Agents Detailed information on other adventitious agents such as bacteria, mycoplasmas, and fungi should be submitted in the appropriate sections of the main dossier. A.3 Excipients In accordance with the relevant clinical trial phase, the information specified in section 2.S should be submitted for novel excipients. A.4 Reconstitution and Dilution Solvents Where applicable, the relevant information specified in section 2.P should be submitted for reconstitution and dilution solvents. 3. INFORMATION ON THE QUALITY OF BIOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS LICENSED BY THE COMPETENT AUTHORITIES WITHOUT MODIFICATION OF THE REGULATORY INFORMATION Where the test and comparator products to be used in the clinical trial are licensed by the competent authorities, it will be sufficient to submit the name of the marketing authorisation holder and the marketing authorisation number (including equivalent information such as a copy of the summary of product characteristics / product information or prescribing information). For modified licensed investigational medicinal

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products, refer to the following section (Section 4). For unmodified licensed 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 performed without changing the primary packaging, the following information must be included in the simplified investigational medicinal product dossier, in addition to the requirements listed in Section 3 of the Guideline on Chemical and Pharmaceutical Quality Requirements for Medicinal Products for Human Use Used in Clinical Trials: - Information guaranteeing that the investigational medicinal product possesses the appropriate identity, assay, quality, and purity attributes (e.g., for investigational medicinal products licensed by the competent authorities, reference to the summary of product characteristics), - Information on the facility where repackaging/relabeling operations are performed. For test and comparator products not licensed by the competent authorities, a complete application should be submitted in accordance with the requirements specified in Section 2 of this guideline. 4. INFORMATION ON THE QUALITY OF BIOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS LICENSED BY THE COMPETENT AUTHORITIES WITH MODIFICATION OF THE REGULATORY INFORMATION The information to be submitted in the investigational medicinal product dossier regarding test and comparator products licensed by the competent authorities with modification of the regulatory information (modified) should meet the requirements specified in this guideline. For sections not affected by the modification, reference may be made to the medicinal product for human use licensed by the competent authorities.

5. INFORMATION ON THE CHEMICAL AND PHARMACEUTICAL QUALITY OF PLACEBO PRODUCTS The information to be submitted in the investigational medicinal product dossier regarding placebo products should meet the requirements specified in Section 6 of the Guideline on Chemical and Pharmaceutical Quality Requirements for Medicinal Products for Human Use Used in Clinical Trials. 6. SUBSTANTIAL AND NON-SUBSTANTIAL MODIFICATIONS MADE TO THE INVESTIGATIONAL MEDICINAL PRODUCT DOSSIER In accordance with Good Manufacturing Practices (GMP), Product Specification Files should be maintained at the relevant facility for each investigational medicinal product and auxiliary medicinal product for human use, and should be continuously updated to ensure traceability throughout the product development process. After the trial authorisation has been obtained, modifications to the trial may be permitted. A modification may take the form of an update to existing information and documents or the addition of new information and documents. Any modification to any aspect of the trial made after the trial authorisation that may have a significant impact on the safety and rights of the volunteers 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 non-substantial modifications. When evaluating the investigational medicinal product dossier, the focus should be on patient safety. Therefore, any modification involving a potential new risk should be considered a substantial modification. Substantial modifications particularly cover situations relating to changes in the impurity profile, microbial contamination, viral safety, TSE modifications, and situations where toxic degradation products may be formed. Where the investigational medicinal product dossier is updated, a new investigational medicinal product dossier with an updated date and, where applicable, version number, along with a document indicating the modifications, should be submitted to the ethics committee and the Agency. Furthermore, for updates made to the investigational medicinal product dossier, a table containing the current/proposed form of the modification, its justification, and the relevant article number for the modification set out in Annex-1 must also be appended to the application. The template table to be appended to the application is provided in Annex-2. 7. ENTRY INTO FORCE This guideline enters into force as of the date of its publication. 8. EXECUTION This guideline is executed by the President of the Agency.

References 1. REGULATION ON CLINICAL TRIALS OF HUMAN MEDICINAL PRODUCTS published in the Official Gazette dated 27/05/2023 and numbered 32203 2. REGULATION ON

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MEDICAL DEVICE CLINICAL TRIALS published in the Official Gazette dated 08/07/2022 and numbered 31890 3. GOOD CLINICAL PRACTICE GUIDELINE 4. CTD GUIDELINE 5. GOOD MANUFACTURING PRACTICES (GMP) GUIDELINE FOR HUMAN MEDICINAL PRODUCT MANUFACTURING SITES 6. GUIDELINES ON VIRUS SAFETY EVALUATION OF BIOTECHNOLOGICAL INVESTIGATIONAL MEDICINAL PRODUCTS (EMEA/CHMP/BWP/398498/05) 7. STRATEGIES TO IDENTIFY AND MITIGATE RISKS FOR FIRST-IN-HUMAN CLINICAL TRIALS WITH INVESTIGATIONAL MEDICINAL PRODUCTS (EMEA/CHMP/SWP/28367/07) 8. ICH: VIRAL SAFETY EVALUATION OF BIOTECHNOLOGY PRODUCTS DERIVED FROM CELL LINES OF HUMAN OR ANIMAL ORIGIN Q5A(R1) 9. ICH: QUALITY OF BIOTECHNOLOGICAL PRODUCTS: ANALYSIS OF THE EXPRESSION CONSTRUCT IN CELLS USED FOR PRODUCTION OF R-DNA DERIVED PROTEIN PRODUCTS Q5B 10. ICH: QUALITY OF BIO TECHNOLOGICAL PRODUCTS: STABILITY TESTING OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS Q5C 11. ICH: DERIVATION AND CHARACTERISATION OF CELL SUBSTRATES USED FOR PRODUCTION OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS Q5D 12. ICH: COMPARABILITY OF BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS Q5E 13. ICH: DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES) Q11 14. ICH: VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY Q2(R1) 15. ICH: SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS Q6B 16. ICH: GUIDANCE ON NONCLINICAL SAFETY STUDIES FOR THE CONDUCT OF HUMAN CLINICAL TRIALS AND MARKETING AUTHORIZATION FOR PHARMACEUTICALS M3(R2) 17. ICH: PRECLINICAL SAFETY EVALUATION OF BIOTECHNOLOGY-DERIVED PHARMACEUTICALS S6(R1) 18. ICH: ASSESSMENT AND CONTROL OF DNA REACTIVE (MUTAGENIC) IMPURITIES IN PHARMACEUTICALS TO LIMIT POTENTIAL CARCINOGENIC RISK M7(R2) 19. NOTE FOR GUIDANCE ON MINIMISING THE RISK OF TRANSMITTING ANIMAL SPONGIFORM ENCEPHALOPATHY AGENTS VIA HUMAN AND VETERINARY MEDICINAL PRODUCTS (EMA/410/01 Rev.3) 20. ANNEX II TO NOTE FOR GUIDANCE ON PROCESS VALIDATION: NON-STANDARD PROCESSES (CPMP/QWP/2054/03)

ANNEXES ANNEX-1 CHANGES MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT FILE CHANGES MADE IN THE INVESTIGATIONAL MEDICINAL PRODUCT FILE Justification Type of Change

Major Change (1) Change (2) 1. Changes in the Manufacturer(s) of the Active Substance 1.1.1. Any addition to section S.2.1. Addition or change of a new manufacturer, manufacturing or testing facility (a different company or a facility of the same company at a different location) 1.1.2. Removal of a manufacturing or testing facility (due to quality/safety reasons or non-compliance with GMP requirements)

1.2.1. Removal of a manufacturing or testing facility (not arising from quality/safety reasons) 1.2.2. Change in the name of the manufacturer

2. Changes in the Manufacturing Process of the Active Substance 2.1.1. New expression cell line 2.1.2. New master cell bank 2.1.3. Establishment of a working cell bank in case it is prepared from an approved master cell bank 2.1.4. Change of a raw material of biological origin 2.1.5. Changes in viral safety tests applied to cell banks or unprocessed bulk batches 2.1.6. Change in batch size of the manufacturing bioreactor (upstream process) 2.1.7. Changes in cell culture conditions that potentially affect quality characteristics 2.1.8. Changes in the purification process (downstream): addition or removal of a purification step 2.1.9. Changes in process conditions of any step that is determined to contribute to virus removal/inactivation or that requires new virus validation studies 2.2.1. Addition or increased frequency of in-process controls (not arising from safety reasons) 2.2.2. Changes in process parameters demonstrated to have no effect on product quality (same process, similar raw materials) 2.2.3. Repetition of a process provided that it was adequately described and accepted in the investigational medicinal product file at the initial application 2.2.4. Minor changes in the manufacturing process that do not require comparability studies 2.2.5. Changes made in the controls of non-critical raw materials

2.1.10. Repetition of any process (not specified in the investigational medicinal product file) 2.1.11. Changes that would lead to the emergence of new impurities or related substances

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3. Changes in the Specifications of the Active Substance 3.1.1. Changes in specifications (deletion of a specification parameter or widening of acceptance criteria)

3.1.2. Addition of specification parameter(s) arising from safety/quality reasons 3.2.1. Addition of a specification parameter or narrowing of acceptance criteria, not arising from safety/quality reasons 3.2.2. Addition, deletion, or modification of a specification parameter due to updates made in pharmacopoeia monographs 4. Changes in Analytical Methods Used in the Control of the Active Substance 4.1.1. Addition of a new test method 4.1.2. Modification of the method in a manner that will affect existing analytical method performance parameters 4.2.1. Improvement of the same analytical method (such as higher sensitivity, precision, accuracy) provided that the following conditions are met I. Acceptance criteria being the same or narrower II. The improved method being suitable for use or validated depending on the development stage and yielding comparable or superior validation results 4.2.2. Making minor changes to the method in a manner that will not affect existing analytical method performance parameters 4.2.3. Updating test procedures for the purpose of compliance with updates made in pharmacopoeia monographs

5. Active Substance Batch Analyses 5.2.1. Submission of data for additional batches manufactured using the same process specified in the investigational medicinal product file, unless otherwise requested 6. Reference Standard Change 6.1.1. Use of a new reference standard for a biological/biotechnological active substance

6.2.1. Use of a new reference standard for a biological/biotechnological active substance, provided that the new reference standard is manufactured using the same manufacturing process as the current reference standard and is qualified in accordance with the approved qualification protocol 6.2.2. Use of a new reference standard for a chemical compound, provided that equivalence with the previous reference standard has been demonstrated 7. Changes in the Container Closure System of the Active Substance 7.1.1. Container closure system change that may affect the stability of the active substance (such as contact material, surface/volume ratio) 7.2.1. Change in the supplier of packaging components provided that the material is the same and of equivalent quality (e.g., same standard quality) 8. Changes Related to the Stability of the Active Substance 8.1.1. Changes in approved storage conditions 8.1.2. Changes in the approved stability protocol 8.2.1. Addition of intermediate points to stability time points for the purpose of increasing the frequency of intermediate analyses without changing the extrapolation conditions (for example, addition of a 42-month stability time point)

8.1.3. Extension of shelf life outside the approved stability protocol or without prior commitment 8.1.4. Shortening of shelf life arising from safety/quality reasons

8.2.2. Shortening of shelf life not arising from safety/quality reasons 8.2.3. Shelf life extension carried out provided that the following conditions are fulfilled: I. The maximum shelf life after extension shall not exceed twice the period covered by real-time stability data and shall not exceed twelve months, and shall not go beyond the period specified in the approved stability protocol. II. The shelf life extension carried out shall be within the scope of the approved stability protocol and in compliance with the protocol. III. In the ongoing stability study results at the storage temperature specified in the stability protocol; any out-of-specification result or any significant trend that could lead to out-of-specification results throughout the approved shelf life shall not have been detected.

9. Changes in the Formulation of the Investigational Medicinal Product 9.1.1 Changes in the qualitative and quantitative composition of the formulation, including changes made in the active substance concentration and excipient composition

10. Changes in the Manufacturers of the Investigational Medicinal Product 10.1.1 Addition or change of a manufacturing/packaging/testing facility 10.1.2 Removal of a manufacturing/packaging/testing facility (due to quality/safety reasons or non-compliance with GMP requirements) 10.1.3 Addition or change of a batch release site

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10.2.1. Removal of a manufacturing, packaging, or testing facility (not arising from quality/safety reasons) 10.2.2. Manufacturer name change 10.2.3. Addition or change of an import facility that does not have a batch release site and holds a valid GMP certificate 11. Changes in the Manufacturing Process of the Investigational Medicinal Product 11.1.1 Major changes in the manufacturing process and critical process controls (e.g., bioburden limit)

11.2.1. Changes in process (same process) parameters in cases where it has been demonstrated that there is no effect on product quality 11.2.2. Increase in batch size of the filling process provided that it is supported by appropriate media fill studies 12. Changes in the Specifications of the Investigational Medicinal Product (Release and Shelf Life Specifications) 12.1.1. Widening of acceptance criteria or deletion of a specification parameter 12.1.2. Addition of a specification parameter or acceptance criterion arising from safety/quality reasons 12.2.1. Narrowing of acceptance criteria (not arising from safety/quality reasons) 12.2.2. Addition of a specification parameter (not arising from safety/quality reasons) 13. Changes in Analytical Methods Used in the Control of the Investigational Medicinal Product 13.1.1. Addition of a new test method 13.1.2. Modification of the method in a manner that will affect existing analytical method performance parameters 13.2.1. Improvement of the same analytical method (such as higher sensitivity, precision, accuracy) provided that the following conditions are met I. Acceptance criteria being the same or narrower

II. The improved method being validated depending on its suitability for use or its stage of development, and yielding comparable or superior validation results 13.2.2. Making minor changes to the method in such a way as not to affect the performance parameters of the current analytical method 13.2.3. Updating test procedures in order to ensure compliance with the updates made in pharmacopoeia monographs

14. Batch Analyses of the Investigational Product 14.2.1 Unless otherwise requested, submission of data for additional batches manufactured using the same process specified in the investigational product file

15. Change in the Container Closure System of the Investigational Product 16.1.1. Making changes in the primary packaging 15.2.1 Making changes in the secondary packaging 15.2.2 Change of the supplier (addition, deletion, replacement) of the primary packaging components, provided that the material remains the same and the specifications are at least equivalent 16. Changes to Medical Devices 16.1.1. Addition/replacement (replacement)/modification of a medical device having a potential impact on quality, safety and/or efficacy 16.2.1. Addition/replacement (replacement)/modification of a medical device considered to have no impact on quality, safety and/or efficacy 17. Change in the Stability of the Investigational Product 17.1.1. Making changes to the approved stability protocol 17.1.2. Making changes to the approved in-use stability information 17.1.3. Extension of the shelf life outside the approved stability protocol or without prior commitment 17.1.4. Shortening of the shelf life due to safety/quality reasons

17.2.1. Addition of intermediate points to the stability time points in order to increase the frequency of interim analyses without changing the extrapolation conditions (e.g., addition of the 42-month stability time point) 17.2.2. Shortening of the shelf life not arising from safety/quality reasons 17.2.3. Shelf life extension performed provided that the following conditions are fulfilled: I. The maximum shelf life following the extension shall not be more than twice the period covered by real-time stability data and shall not be more than twelve months, and shall not go beyond the period specified in the approved stability protocol. II. The shelf life extension made shall be within the scope of the approved stability protocol and in accordance with the protocol. III. In the ongoing stability study results under the storage temperature set out in the stability design; no out-of-specification result or any significant trend that could give rise to out-of-specification results throughout the approved shelf life shall have been detected.

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

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Corresponding to the Relevant Change

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