GUIDELINE ON BIOSIMILAR MEDICINAL PRODUCTS SECTION 1 OBJECTIVE, SCOPE, LEGAL BASIS AND DEFINITIONS Objective

ARTICLE 1- (1) The objective of this guideline is to define the concept of biosimilar medicinal product and to establish the general principles to be applied as the basis for the authorization of these products.

Scope

ARTICLE 2 – (1) This guideline summarizes the general principles applicable to similar biological medicinal products, also known as biosimilars, and sets out the principles for demonstrating biosimilarity. (2) This guideline clarifies the quality, non-clinical and clinical requirements for demonstrating the comparability of biosimilar medicinal products containing recombinant DNA-derived proteins and their derivatives. (3) The principles described in this guideline may also be applicable to other biological products (e.g., low-molecular-weight heparins). (4) Current national/international guidelines specific to the product and product class shall complement this guideline. (5) Applicants may consult the Agency if they require more detailed information than that available in the guidelines when developing biosimilar medicinal products.

Legal Basis

ARTICLE 3- (1) This guideline has been prepared based on the Regulation on the Licensing of Human Medicinal Products, which entered into force upon its publication in the Official Gazette dated 19/01/2005 and numbered 25705.

Definitions

ARTICLE 4- (1) In this Guideline; 1) Biological Medicinal Product: A human medicinal product whose active substance or substances are produced in a biological source or purified from a biological source, and whose quality, manufacturing process and controls are demonstrated by physicochemical and biological tests together,

2) Biosimilar Medicinal Product: A human medicinal product that exhibits a high degree of similarity to a licensed biological reference medicinal product, .

3) Pharmacopoeia: The Turkish Pharmacopoeia, the European Pharmacopoeia, the United States Pharmacopoeia and the Japanese Pharmacopoeia, 4) Guideline: The Guideline on Biosimilar Medicinal Products, 5) Agency: The Turkish Medicines and Medical Devices Agency (TİTCK),

6) Reference Medicinal Product: A biological medicinal product licensed with a full dossier for first-time marketing in the world, having been proven by the Agency or by the competent authorities of ICH (International Council for Harmonisation) founding or permanent members to possess scientifically acceptable efficacy, quality and safety, 7) Comparator Medicinal Product: A biological medicinal product licensed with a full dossier for first-time marketing in the world, having been proven by the Agency or by the competent authorities of ICH founding members, permanent members and/or authorities other than permanent members to possess scientifically acceptable efficacy, quality and safety,

shall be meant.

SECTION 2

GENERAL PRINCIPLES

Application of the Biosimilar Approach

ARTICLE 5 – (1) In the application of the biosimilar approach, similarity to the reference medicinal product in terms of quality, safety and efficacy must be demonstrated on the basis of a comprehensive comparability exercise.

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(2) The concept of biosimilarity is, in principle, applicable to all biological medicinal products. In practice, successfully developing a biosimilar medicinal product depends on the capability to produce a medicinal product similar to the reference medicinal product and on demonstrating the similarity of the products concerned. Therefore, the application dossier includes comprehensive physicochemical and biological characterization along with safety and efficacy comparability studies.

(3) Where, as a result of biosimilar comparability analyses, data are obtained that render biosimilarity impossible, or where significant differences exist between the biosimilar and the reference medicinal product and these differences cannot be clinically justified, similarity to the reference medicinal product cannot be at issue, and the biosimilar marketing authorisation application shall not be considered appropriate.

(4) The detailed quality and comparability data presented in the dossier of the biosimilar medicinal product also include the analytical methods used, physicochemical characterization, biological activity, purity/impurities and valid specifications.

(5) In the application dossier, the comparability studies are presented in the quality-related module as a separate section (CTD Module 3.2.R – Regional Information).

(6) Comparability studies at the quality level shall be performed for the active substance and the finished product using analytical and bioanalytical methods of adequate sensitivity, and shall cover the relevant quality attributes. However, where the formulation of the finished product is such that it interferes with the analysis of the active substance, the comparison studies shall be conducted separately for both the active substance and the finished product. Where the reference active substance used for characterization has been isolated from a formulated reference preparation, it shall be demonstrated that the active substance is not altered by the isolation procedure.

(7) Biosimilar medicinal products shall be manufactured and controlled in a manner appropriate to the pharmaceutical development of the product, using current methods described in pharmacopoeias and/or other sources.

(8) When manufacturing a biosimilar medicinal product, the manufacturer may not have access to detailed information on the reference medicinal product and its manufacturing processes. Nevertheless, the analytical data presented shall be at a level sufficient to demonstrate the similarities and differences between the reference medicinal product and the biosimilar medicinal product from the physicochemical and biological perspectives.

(9) The non-clinical section covers the pharmaco-toxicological assessment, while the clinical section covers the requirements for pharmacokinetic, pharmacodynamic and efficacy studies. The section of this guideline on clinical safety and pharmacovigilance includes clinical safety studies, including immunogenicity. In the guideline, it is recommended that non-clinical and clinical studies be conducted in a sequential manner.

(10) Depending on the structure and complexity of the reference medicinal product, the extent of the non-clinical and clinical studies to be conducted in order to demonstrate biosimilarity may vary. Differences identified in the physicochemical and biological analyses of the biosimilar medicinal product will guide the planning of the non-clinical and clinical studies. All approved indications of the reference medicinal product, the related mechanism(s) of action [the relevant receptor(s), etc.] and its immunogenicity constitute points that require attention.

(11) Where there is any difference between the biosimilar medicinal product and the reference medicinal product, information on the origin of this difference and how it is to be interpreted must be presented in the application dossier. In this approach:

a) Due to the complexity of biological/biotechnological medicinal products, in terms of demonstrating biosimilarity, the standard generic approach, which encompasses bioavailability and bioequivalence studies for chemical medicinal products for human use, is not appropriate. For this reason, the biosimilar approach based on comprehensive comparability studies must be followed.

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b) The principles of biosimilar comparability studies are the same as the scientific principles applied in comparability studies for changes made to the manufacturing process of a biological medicinal product.

c) Whether the biosimilar approach is applicable to a particular biological medicinal product, and its comparability, depend on the clinical models used for assessment, state-of-the-art analytical methods and the manufacturing processes employed.

d) The biosimilar approach can be more successfully applied to products that are highly purified and can be characterized in detail. The application of the biosimilar approach to products that are inherently more difficult to characterize is more challenging. Examples of such products include biological medicinal products prepared with active substances obtained by purification from biological sources and/or biological medicinal products for which regulatory and clinical experience is limited.

e) The active substance of the biosimilar medicinal product must be highly similar to the active substance of the reference medicinal product in molecular and biological terms.

f) The posology and route of administration of the biosimilar and the reference medicinal product must be the same.

g) Where the pharmaceutical form, strength, formulation, excipients of the biosimilar medicinal product, or the presentation of the pharmaceutical form differ from those of the reference product, the relevant difference must be justified with additional data. Any difference must not create a safety risk.

h) Changes made with the aim of improving efficacy are not compatible with the biosimilar approach. However, differences that may confer an advantage in terms of safety (for example, lower levels of impurities or lower immunogenicity) do not preclude biosimilarity.

i) With respect to quality data, a biosimilar medicinal product must meet all current requirements for CTD Module 3, including the technical requirements of the pharmacopoeia and any additional requirements defined in the relevant guidelines.

Selection of the Reference Medicinal Product

ARTICLE 6 – (1) The use of the reference medicinal product in biosimilarity studies is recommended. However, in order to facilitate the global development of biosimilar medicinal products and to avoid unnecessary repetition of clinical trials, the use of a comparator medicinal product in biosimilarity studies may be accepted, provided that all of the conditions specified below are met. a) The quality-level comparative studies of the biosimilar medicinal product should include a side-by-side analysis of the reference medicinal product and the biosimilar medicinal product. However, the joint use of the reference and comparator medicinal products may be accepted during the development of the Target Product Quality Profile (TPQP) of the biosimilar medicinal product. b) Where, during the development stage, certain in vivo non-clinical and clinical studies have been conducted with the comparator medicinal product, the applicant should scientifically justify the suitability of these comparative data and provide sufficient data to establish an acceptable bridge to the reference medicinal product. Scientifically, the required bridging data should include data obtained from analytical studies (e.g., structural and functional data) comparing all three products (biosimilar, reference and comparator medicinal products). However, it may also include data obtained from clinical PK and/or PD bridging studies for the three products. The overall acceptability of such an approach and the type of bridging data required may vary depending on the product. The Agency may be consulted on this matter if needed. The final determination of the scientific justification and the adequacy of the bridge is made only during the evaluation of the application.

(2) No biosimilar medicinal product may serve as a reference medicinal product.

(3) The brand name, pharmaceutical form, formulation, manufacturing date, strength, manufacturing site, batch number and expiry date of the reference medicinal product used in the comparative study must be clearly stated.

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(4) The same reference medicinal product is used for the quality, non-clinical and clinical sections of the dossier. Where a comparator product is used, as stipulated in the first paragraph of this Article, this requirement is also considered fulfilled. In cases where the name of the reference medicinal product varies from country to country, this situation should be justified. (5) Reference standards included in pharmacopoeias cannot be used as the reference medicinal product. However, it is appropriate to use these reference standards during analytical development. (6) In cases where the reference medicinal product is available in different strengths, in principle, the same strength as that of the biosimilar medicinal product to be compared is selected. If a different strength is selected, this situation should be duly justified.

Principles for Demonstrating Biosimilarity

ARTICLE 7 – (1) The fundamental principle of the biosimilar medicinal product development programme is to establish the similarity between the biosimilar medicinal product and the reference medicinal product by means of sensitive and complementary methods, with the aim of demonstrating that the previously proven safety and efficacy of the reference medicinal product also apply to the biosimilar.

(2) The biosimilar medicinal product should be highly similar to the reference medicinal product in physicochemical and biological terms. The analyses to be performed should include comparative studies. Any difference identified must be justified in terms of its potential effects on safety and efficacy.

(3) A stepwise approach is recommended throughout the development programme, beginning with comprehensive physicochemical and biological characterisation studies. The extent and nature of the non-clinical in vivo and clinical studies to be conducted depend on the robustness of the physicochemical, biological/non-clinical in vitro data and on the evidence obtained in previous steps.

(4) In general, the purpose of the clinical trials is to demonstrate the comparable clinical performance of the biosimilar medicinal product and the reference medicinal product, taking into account any minor differences observed in earlier steps. However, clinical data cannot be used to justify significant differences in quality attributes.

(5) In biosimilar comparability exercises, the goal is to eliminate, as far as possible, differences between the biosimilar medicinal product and the reference medicinal product. Therefore,

the studies should be sufficiently sensitive in terms of design, methods, endpoints and/or study population to detect such differences.

(6) It is appropriate to avoid unnecessary repetition of clinical trials. Consequently, a confirmatory clinical trial may not be required under specific conditions. This condition applies to cases where the similarity of efficacy and safety can be clearly demonstrated by the physicochemical characteristics, biological activity/potency and pharmacokinetic and/or pharmacodynamic profiles of the biosimilar and the reference medicinal product. However, this condition cannot be applied in cases where there are differences in the impurity profile or in the composition of the excipients of the biosimilar medicinal product.

SECTION 3

QUALITY

Manufacturing Process of the Similar Biological Medicinal Product

ARTICLE 8- (1) The development and documentation process of a biosimilar medicinal product shall cover the following: a) The Target Product Quality Profile (TPQP) and the molecule characteristics shall be comparable to the reference medicinal product. b) The performance of the manufacturing process of the biosimilar medicinal product shall be specific to the product itself and consistent.

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(2) The TPQP of a biosimilar medicinal product shall be based on the information obtained from the selected reference medicinal product, on accessible sources, and on data derived from the extensive characterisation of the reference medicinal product. The TPQP shall form the basis of the development of the biosimilar medicinal product and of its manufacturing operations.

(3) The biosimilar medicinal product shall be manufactured and controlled in a manner appropriate to its own development, taking into account state-of-the-art technologies and knowledge in manufacturing processes and the product characteristics. As is the case for every biological medicinal product, the biosimilar medicinal product shall be defined by the molecular composition of the active substance resulting from the manufacturing process. When establishing the TPQP, product-specific molecular variants and isoforms arising in the manufacturing process shall be taken into account.

(4) A different expression system may also be used for the biosimilar medicinal product, provided that, when compared with the reference medicinal product, it does not lead to undesirable outcomes such as an atypical glycosylation pattern, high variability, or a different impurity profile.

(5) Data on the development and characterisation of cell banks, including clone stability, together with the Good Manufacturing Practice (GMP) certificates of the manufacturing site of the cell banks shall be submitted.

(6) The development process of each biosimilar medicinal product is specific to that product. Where a change is made to the manufacturing method during the development of the biosimilar medicinal product, a comparability study shall be conducted for the method changes applied during development, comparing the product manufactured with the previous method, and these studies shall be kept separate from the biosimilar comparability exercise.

(7) The formulation of the biosimilar medicinal product shall be selected taking into account technological developments. Although the formulation is not required to be identical to that of the reference medicinal product, the suitability, stability, and compatibility of the formulation (with excipients, diluents, and packaging materials), as well as the integrity, efficacy, and potency of the active substance shall be demonstrated through detailed analyses to be performed.

(8) Studies demonstrating the quality comparability of the biosimilar medicinal product shall be conducted throughout the entire development process of the product and on commercial batches. If a formulation and/or container-closure system different from the reference medicinal product has been selected (in case of any material in contact with the product), it shall be verified that this has no impact on the quality, efficacy, and safety of the biosimilar medicinal product.

(9) The stability of the biosimilar medicinal product shall be determined in accordance with the relevant guidelines. The adequacy of the stability shall be demonstrated with data obtained from studies. Performing stability studies by extrapolation from the reference medicinal product is not appropriate.

Biosimilar Comparability Exercise

ARTICLE 9 - (1) In order to ensure that consistent data are obtained during the development of a biosimilar medicinal product, for all quality, safety, and efficacy studies, different batches of the reference medicinal product shall be compared simultaneously and under the same conditions with different batches of the biosimilar medicinal product. In order to generate quality data, the TPQP of the biosimilar medicinal product shall be determined using at least 3 different batches of the reference medicinal product in comparability exercises with the biosimilar medicinal product. When determining the TPQP, it is recommended that at least 3 different batches of the reference medicinal product be selected at different ages.

(2) In order to demonstrate biosimilar comparability at the quality level, it is recommended that the development processes of the biosimilar medicinal product be conducted in at least 3 different batches at different stages. A comparative analysis of at least 3 batches manufactured at a scale appropriate to the process at a qualified manufacturing site, with at least 3 different

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batches of the reference medicinal product, shall be submitted. These analyses shall cover structural and functional data.

(3) Where the applicant justifies that different reference product batches were not available during product development, the requirement to compare with at least 3 different batches of the reference product may not be sought.

ARTICLE 11 - (1) The comparability exercise of the biosimilar medicinal product with the reference medicinal product shall be presented comprehensively, including the primary, secondary, and tertiary structure and the glycosylation (PTMs) profile.

(2) The aim of comparability exercises is to demonstrate that the biosimilar medicinal product is similar to the reference medicinal product at the finished product level. The quality characteristics of the biosimilar medicinal product are not expected to be identical in all respects to those of the reference medicinal product. However, where quantitative and/or qualitative differences exist, these differences shall be justified and it shall be demonstrated that this situation has no impact on the clinical performance of the product. In such cases, additional non-clinical and/or clinical data may be required. In particular, quality characteristics that have an impact on immunogenicity/potency or that are not observed in the reference medicinal product shall be taken into consideration.

(3) Although minimised, process-related impurities may differ between the reference and biosimilar medicinal products. Lower levels that may provide a safety advantage with respect to impurities do not preclude biosimilarity.

(4) Where possible, quantitative ranges shall be established for the biosimilar comparability exercise. These ranges shall primarily be based on the measured quality attributes of the reference medicinal product and, unless otherwise justified, shall not be wider than the variability range of the representative reference medicinal product batches. The adequacy of the ranges shall be discussed taking into account the number of reference medicinal product batches tested, the quality attribute investigated, the age of the batches at the time of testing, and the test method used. A descriptive statistical approach may be used for the purpose of establishing ranges for quality attributes, provided it is appropriately justified.

(5) It shall be noted that the acceptable ranges used for the biosimilar comparability exercise against the reference medicinal product shall be addressed separately from the release specifications.

(6) The manufacturing process of the reference medicinal product may change over time in a manner that leads to detectable differences in its TPQP. This may also occur while a biosimilar medicinal product is being developed. Ranges relating to deviations in the quality profile before and after such changes observed in the reference medicinal product may be used to support the biosimilar comparability exercise at the quality level. Quality attributes falling within or outside the ranges established for a quality attribute of the reference medicinal product shall be verified in terms of their potential impact on safety and efficacy. Once a biosimilar medicinal product has been authorised, there is no need to re-demonstrate biosimilarity.

Analytical Evaluation

Article 12 - (1) Comprehensive characterization studies shall be carried out in parallel with one another using advanced technological methods in order to guarantee that the biosimilar and the reference medicinal product are comparable in terms of quality. It is the responsibility of the applicant to demonstrate that the methods selected for use in comparability exercises are capable of detecting any small differences in the quality assessment (e.g., high-sensitivity detection of relevant variants). The methods used in characterization studies constitute an integral part of the quality data package. These methods shall be suitable for the purpose of comparability and shall be validated in accordance with the guidelines. Where available, standards and reference materials (e.g., pharmacopoeial standards, WHO standards) shall be used for method suitability and standardization.

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(2) Certain analytical methods may not be suitable for, or may provide limited information on, the direct or parallel analysis of the biosimilar and the reference medicinal product (e.g., in cases where the active substance is present at low concentrations and/or excipients that may interact, such as albumin, are present). Therefore, samples may be taken from the finished product (e.g., by extraction, concentration and/or other suitable techniques). In such cases, the techniques used to prepare the samples shall be outlined, and their effect on the samples shall be appropriately stated and discussed (e.g., comparison of the active substances before and after preparation).

a) Physicochemical Properties:

I- The physicochemical comparison shall include the evaluation of physicochemical parameters and the structural determination of product-related substances and impurities. The physicochemical characterization programme shall include the determination of the composition, physical properties, and primary and higher-order structures of the active substance in the biosimilar medicinal product. The intended amino acid sequence of the biosimilar medicinal product shall be confirmed and shall be identical to that of the reference medicinal product. II- The N- and C-terminal amino acid sequences, free -SH groups, and disulphide bridges shall be compared by appropriate methods. The quantity of modifications and truncations in the protein shall be measured and, where process-specific or expression-system-related variables exist, they shall be explained. III- Differences detected between the biosimilar and the reference medicinal product (for example, C-terminal lysine variability) shall be justified with regard to the microheterogeneous nature of the reference medicinal product. IV- Structural differences occur naturally in proteins during biosynthesis. For this reason, the biosimilar medicinal product may contain a mixture of post-translational modification forms (glycosylation, oxidation, deamidation, truncation, etc.). V- The presence and extent of post-translational modifications (e.g., glycosylation, oxidation, deamidation, truncation, etc.) shall be characterized by appropriate methods. VI- Where carbohydrate structures are present, the overall glycan profile, the site-specific glycosylation pattern, and the site occupancy shall be compared in detail. VII- Attention shall be paid to the presence of glycosylation patterns or variants not observed in the reference medicinal product, and appropriate justification shall be provided, paying particular attention to structures that are not found in humans (non-human linkages, sequences, or sugars). VIII- In order to guarantee the consistency of the manufacturing process of each biosimilar medicinal product and the stability of the final product, a robust quality control and quality assurance system shall be established, and all validation operations carried out during the process shall be presented in detail in the file.

b) Biological Activity

I- The biosimilar comparability exercise shall include, as a core step, the evaluation of the biological properties of the biosimilar and the reference medicinal product in order to establish a complete characterization profile. II- Biological activity is the specific ability or capacity of the product to achieve a defined biological effect. Different and complementary approaches shall be used to measure biological activity. Depending on the biological properties of the product and the limitations of the analytical methods, different assays may be used (e.g., ligand or receptor binding assays, enzymatic assays, cell-based assays, functional assays, etc.). III- Where applicable, different assays shall be used to evaluate receptor binding and activation. Under appropriate conditions, cross-reference may be made to the non-clinical and/or clinical parts of the application dossier. It shall be demonstrated that the biological assays are sufficiently sensitive, specific, and adequately discriminating. The results of valid biological assays shall, where available and appropriate, be expressed in units of activity calibrated against a national or international reference standard. Where applicable, these assays shall comply with the relevant Pharmacopoeial requirements for biological assays.

c) Immunochemical Properties

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I- The immunological functions of monoclonal antibodies and related substances (such as fusion proteins made with the IgG Fc portion) shall be fully compared with the reference medicinal product. In this regard, the affinity of the products for the intended target shall be compared. II- In addition, the binding affinity of the Fc for relevant receptors (for example, FcγR, C1q, FcRn) shall also be compared unless otherwise justified. Furthermore, appropriate methods shall be used to compare the ability to trigger Fab- and Fc-related effector functions.

ç) Purity and Impurities I- The purity and impurity profiles of the biosimilar and the reference medicinal product shall be compared, both qualitatively and quantitatively, using a combination of different analytical procedures. In addition to orthogonal methods, complementary and state-of-the-art methods shall be used to identify and compare product-related substances and impurities. In this comparison, the specific degradation pathways of the biosimilar medicinal product (e.g., oxidation, deamidation, aggregation) and the possible post-translational modifications of proteins shall be taken into consideration. II- During the tests conducted, the age/shelf-life of the reference medicinal product shall be stated and its possible impact on the quality profile shall be explained. A comparison of the relevant quality attributes tested at selected time points and under storage conditions (e.g., accelerated or stress conditions) may be used to support the similarity of the degradation pathways of the reference and biosimilar medicinal products. III- Process-related impurities (e.g., host cell proteins, host cell DNA, reagents, purification-related impurities, etc.) may differ qualitatively from process to process. Therefore, the biosimilar comparability exercise may not be fully related to the qualitative comparison of these parameters. Nevertheless, using current analytical methods in the existing guidelines and pharmacopoeias, the potential risks related to these impurities (e.g., immunogenicity) shall be demonstrated and justified.

d) Quantity: The quantity of the biosimilar medicinal product shall be determined using a suitable assay method and expressed using the same units as the reference medicinal product. The comparability of losses shall be verified for the biosimilar and the reference medicinal product.

Specifications

ARTICLE 13 - (1) With respect to any biotechnology-derived product, the selection of tests to be included in the specifications (or in the control strategy) for the active substance and finished product shall be product-specific and shall be described as set out in the guideline/pharmacopoeia. (2) The proposed acceptance criteria ranges for routine tests shall be justified.

(3) The requested shelf life of the product shall be confirmed with real-time stability data obtained with the biosimilar medicinal product. Comparative, real-time, real-condition-based stability studies between the biosimilar and reference medicinal products are not required.

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SECTION 4
Non-Clinical Studies

ARTICLE 14- (1) Before initiating clinical trials to support biosimilarity, the relevant non-clinical studies shall be conducted. (2) The extent of non-clinical data varies depending on various clinical parameters such as product class, therapeutic index and indication. For all biosimilar medicinal products, the results of comparative non-clinical studies with the reference medicinal product shall be submitted. (3) A stepwise approach is recommended to evaluate the similarity between the biosimilar and the reference medicinal product. First, analytical studies and in vitro pharmacotoxicological studies shall be conducted. Subsequently, a decision shall be made as to the extent to which in vivo animal studies are necessary. (4) For the design of the non-clinical study programme, a clear understanding of the characteristics of the reference medicinal product is required. The results to be obtained from physicochemical and biological characterisation studies (comparative studies of the reference and biosimilar medicinal products) shall be examined in terms of their possible effects on clinical efficacy and safety. (5) The following recommendations shall be evaluated on a product-specific basis, and the approach followed shall be justified in the non-clinical results section.

In Vitro Studies

ARTICLE 15 - (1) In vitro studies constitute the basis of non-clinical comparative tests, as they are generally more specific and sensitive than in vivo animal studies in detecting differences between the biosimilar and the reference medicinal product. (2) Comparative in vitro studies (part of these data may be obtained from quality-related studies) are necessary to reveal potential differences in biological activity between the reference medicinal product and the biosimilar medicinal product. These studies shall include analyses on the following subjects: a) Binding to target(s) (for example receptors, antigens, enzymes) associated with the pharmacotoxicological effects and/or pharmacokinetics of the reference medicinal product. b) Effect on cellular signal transduction pathways and functionality/viability known to be important for the pharmacotoxicological effects of the reference medicinal product. (3) The aforementioned studies shall be conducted with the aim of comparing the effects of the reference medicinal product and the biosimilar medicinal product. Studies in which only the reference medicinal product or only the biosimilar medicinal product is used are not within the scope of the evaluation. The methods used to obtain definitive results shall be suitable for their purposes and scientifically valid. In order to demonstrate that differences detected in quality studies will not be clinically significant, these in vitro studies shall be sensitive, specific and sufficiently discriminating. (4) For the pharmacological target(s) of the reference medicinal product and the biosimilar medicinal product, concentration-activity/binding relationships shall be compared over the concentration range where potential differences will be detected with the greatest sensitivity. (5) The studies shall be conducted with samples from a sufficient number of batches of the reference and biosimilar medicinal products developed for clinical use. Differences between the methods used and between the batches will be decisive in determining the number of samples. The number of tests conducted to compare the reference medicinal product with the biosimilar medicinal product shall be sufficient to demonstrate the similarity of both products. (6) The in vitro studies aimed at demonstrating biosimilarity shall, taken together, cover all pharmacological and toxicological properties of the biosimilar and the reference medicinal product class that may be clinically relevant. The applicant shall discuss, based on the most current scientific data, the extent to which the in vitro tests used in the comparative studies reflect/predict the intended clinical situation.

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Principles for the Assessment of the Need for In Vivo Studies

ARTICLE 16 - (1) Where structural and functional similarity studies within the scope of quality studies are deemed sufficient, biosimilarity is strongly demonstrated by extensive in vitro mechanistic studies, and no condition that could prevent the administration of the medicinal product to humans has been detected, in vivo comparative animal studies may not be required. (2) However, biotechnological products may produce in vivo effects that cannot be determined by in vitro studies. In such cases, appropriate in vivo studies may be necessary to provide complementary data on biosimilarity. (3) Where no non-clinical in vivo study is submitted, the applicant shall justify this. The following factors, without being limited thereto, shall be taken into account in determining the need for in vivo studies;

a) Differences associated with potential quality attributes that cannot be detected in the reference medicinal product, b) Quantitative changes that may cause differences in quality attributes between the reference medicinal product and the biosimilar medicinal product, c) Formulation differences between the reference medicinal product and the biosimilar medicinal product (e.g., in biotechnological products, in the case of the presence of excipients that are not frequently used). Each of these factors alone does not make an in vivo study mandatory; however, these factors shall be considered together when assessing the need for in vivo studies. (4) Where it is concluded that the results obtained from in vitro comparative studies are sufficient and that there is no obligation to conduct in vivo studies, or where the view is formed that the aforementioned factors will not prevent direct transition to human studies, it may be considered that an in vivo animal study is not necessary. (5) Where factors that may affect pharmacokinetics (PK) and/or biodistribution (e.g., increased glycosylation) cannot be sufficiently characterised in quality and in vitro studies, in vivo studies may be necessary. (6) Where there is no clinically relevant animal model for in vivo studies, special animal models (transgenic animals etc.) shall be considered. Where in vivo animal studies cannot be conducted, the applicant may choose to proceed to human studies with measures minimising the potential risks. This situation shall be carefully examined, and all measures shall be taken to reduce potential risks in the decision on the human study. (7) The applicant shall justify its decisions regarding in vivo animal studies on a scientific basis and, where necessary, reach a decision in consultation with the Agency.

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In Vivo Studies

ARTICLE 17 - (1) Where in vivo animal studies are needed to support biosimilarity, the focus of such studies (PK and/or pharmacodynamics (PD) and/or safety) will depend on the additional information required. (2) Animal studies should be designed to obtain the maximum amount of information. (3) The duration of the study (including the observation period) should be planned taking into consideration the pharmacokinetic characteristics of the reference medicinal product and its clinical use. (4) Where the study model allows, the PK and PD of the reference and biosimilar medicinal products should be compared quantitatively, including, where possible, an evaluation of the dose concentration-response covering the intended human exposure. (5) A flexible approach should be considered for safety studies, in particular in cases where non-human primates are the only relevant species that can be used in in vivo studies. Standard repeated-dose toxicity studies in non-human primates are generally not recommended. If appropriately justified, a repeated-dose toxicity study with a modified design (aimed at reducing the number of animals, for example, by using only a single dose of the biosimilar and reference product and/or by conducting the study in only one sex instead of males and females and/or by not using a separate group of animals -recovery group- to determine whether the toxic effects observed in the study are reversible) and/or studies in which safety parameters (such as clinical signs, body weight and vital functions) are assessed in live animals may be conducted. In repeated-dose toxicity studies in which the effect of a single dose will be assessed, the highest possible dose should generally be selected as the upper end of the dose range, and this selection should be justified on the basis of the expected toxicity of the reference medicinal product. (6) Conducting toxicity studies in non-relevant animal species (for example, for the assessment of non-specific toxicity arising solely from impurities) is not recommended. The most appropriate strategy to keep the impurity-related risk to a minimum is to keep the impurity level as low as possible. (7) Qualitative and quantitative differences in product-related variants (for example, changes in the glycosylation profile) may affect the biological functions of such products, and these differences are expected to be evaluated by in vitro tests. In addition, such differences and impurities may affect the immunological potential of biological products and their potential to cause hypersensitivity. It is very difficult to predict such effects by means of animal studies, and such effects should be evaluated in detail in clinical studies. (8) Although immunogenicity assessment in animals is generally not suitable for predicting immunogenicity in humans, these data may be needed for the interpretation of in vivo animal studies. Therefore, where necessary, blood samples from animals should be taken and stored for use in the evaluation of pharmacokinetic/toxicokinetic data. (9) For biosimilar medicinal products, non-clinical testing with respect to pharmacological safety, reproductive toxicity and carcinogenicity is generally not necessary. Local tolerance tests are also generally not required. However, if new excipients have been introduced into the structure of the biosimilar medicinal product and there is no or limited experience with these new excipients in the clinical route of administration through which the product will be used, evaluation of local tolerance may be necessary. If other in vivo studies are to be conducted for biosimilarity, the assessment of local tolerance may be performed as part of the design of those studies without conducting a separate local tolerance study.

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SECTION 5 Clinical Studies

ARTICLE 18 - (1) It is recommended that the clinical data required for biosimilar comparability studies be obtained from biosimilar medicinal products that represent the quality profile of the commercial batches and are manufactured by means of the commercial manufacturing process. In case of non-compliance with this recommendation, this should be justified and supported by sufficient additional bridging data. (2) Clinical comparability studies should follow a stepwise approach; they should begin with pharmacokinetic and, where feasible, pharmacodynamic studies, and then be continued with clinical efficacy and safety studies or, in some specific cases, be followed by confirmatory PK/PD studies to demonstrate the clinical comparability of the biosimilar medicinal product with the reference medicinal product.

Pharmacokinetic Studies

ARTICLE 19 - (1) Comparative pharmacokinetic studies form the basis of clinical comparative studies between the biosimilar medicinal product and the reference medicinal product.

(2) PK studies shall be conducted using the recommended dose range and route of administration for the reference medicinal product. (3) The PK study shall be designed on the basis of the clinical scope, safety and PK characteristics of the reference product (target-mediated clearance, linear or non-linear PK, time-dependency of PK, half-life, etc.) in accordance with the relevant guidelines. Furthermore, bioanalytical assays shall be fit for their intended use and validated methods shall be employed. (4) Prior to the start of the study, biosimilar comparability margins for the primary PK parameters shall be defined and justified. (5) In the absence of specific criteria, the criteria used in standard clinical bioequivalence studies applicable to conventional products may be appropriate for the planning of comparative PK studies of biological products. (6) The interpretation of bioequivalence studies for biological products is more complex than for small molecules. Because while small molecules are assessed as identical, for biological products PK studies are used to detect possible differences in the interactions of the reference and biosimilar medicinal products with the body. This means that observing the ratio of the biosimilar to the reference medicinal product, within predefined and justified acceptance margins, in the 90% confidence interval (CI) alone may not be sufficient. In interpreting similarity, the location and width of the confidence interval shall also be taken into account. For example, in order not to exclude biosimilarity, statistically significant differences within the acceptance margins in the 90% confidence interval for the relevant PK parameters will need to be explained and justified. On the other hand, if similarity exceeds the predefined margins in the 90% confidence interval, the applicant shall investigate and explain the root causes of these differences. If predefined and adequately justified, correction for protein content may be acceptable, assessed on a product basis, together with the analysis results of the biosimilar and reference medicinal products set out in the study protocol. (7) While the importance of target-mediated clearance comparison in the biosimilarity study is known, conducting such comparative studies in patients may not be appropriate, since it would lead to large variability in target expression, including variability in patients over time. However, since comparable interaction between the biosimilar medicinal product and its target(s) (including FcRn for a monoclonal antibody) is expected to be demonstrated by in vitro studies, the absence of a pivotal pharmacokinetic study in the target population may be acceptable if additional pharmacokinetic data are obtained during efficacy, safety and/or pharmacodynamic studies. Because these pharmacokinetic data enable further investigation of the determination of the pharmacokinetic profile in patient subgroups, or through population pharmacokinetics, of variable pharmacokinetics and the clinical impact of possible changes in pharmacokinetics over time. (8) A single-dose crossover design, in which the pharmacokinetic profile, including the late elimination phase, is fully characterized, should be preferred in the studies. (9) The need for a parallel design for substances with a long half-life and/or high immunogenicity risk shall be evaluated. (10) The doses in a single-dose pharmacokinetic biosimilar comparative study conducted in healthy volunteers may be lower than

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the recommended therapeutic doses.

(11) Conducting pharmacokinetic studies in healthy volunteers may not always be appropriate. In such a case, if conducting a single-dose study in patients is not appropriate, the pharmacokinetic evaluation may be part of a multiple-dose study in patients. (12) In the studies, a model/population with fewer factors leading to sensitivity, i.e., major inter-individual or time-dependent variability, shall be investigated. (13) If the reference product can be administered both intravenously and subcutaneously, evaluation of the subcutaneous administration will generally be sufficient, since this situation covers both absorption and elimination. Therefore, if biosimilar comparability has been demonstrated for both absorption and elimination with subcutaneous administration, an exemption from evaluation with intravenous administration is possible. Situations where a pharmacokinetic study for intravenous administration cannot be conducted, for example, where the absorption rate constant of the molecule is much slower than the elimination rate constant (flip-flop kinetics), shall be justified. (14) In single-dose pharmacokinetic studies, the primary parameters shall be AUC(0-∞) for intravenous administration, and AUC(0-∞) and usually Cmax for subcutaneous administration. In these studies, secondary parameters such as Tmax, volume of distribution and half-life shall also be taken into account in the evaluation. (15) In a multiple-dose study, the primary parameters shall be AUC(0-t) covering the time between the first and second administrations, and AUC over one dosing interval at steady state (AUC(0-τ)). The secondary parameters are Cmax at steady state, and Ctrough. (16) In every pharmacokinetic study, anti-drug antibodies shall be measured in parallel with the pharmacokinetic evaluation, using appropriate sampling time points.

Pharmacodynamic Studies

ARTICLE 20 - (1) Where appropriate, the inclusion of pharmacodynamic markers in addition to pharmacokinetic studies is recommended. In studies, pharmacodynamic markers should be selected based on their relationship to the clinical endpoint. (2) Comparative pharmacokinetic/pharmacodynamic studies may be considered sufficient to demonstrate clinical comparability between the biosimilar and the reference medicinal product in certain cases, provided that the conditions set out below are met: a) The selected pharmacodynamic marker/biomarker is an accepted surrogate marker and is related to the patient outcome to such an extent that demonstrating a similar effect on the pharmacodynamic marker will guarantee a similar effect on the clinical outcome. Examples in this regard may include: absolute neutrophil count for evaluating the effect of granulocyte colony-stimulating factor (G-CSF); early viral load reduction in chronic hepatitis C for evaluating the effect of alpha interferons, and the euglycaemic clamp test for comparing two insulins; magnetic resonance imaging of disease lesions may be used for comparing two beta interferons in multiple sclerosis (MS). b) There may also be PD markers that demonstrate the pharmacological effect of the active substance and show a clear dose-response or concentration-response relationship, even though they are not accepted as surrogate markers. In this case, a single or multiple dose-exposure-response study at two or more dose levels may be sufficient for a waiver of the clinical efficacy study. This design ensures that the biosimilar and the reference medicinal product can be compared within the steep part of the dose-response curve. c) A confirmatory clinical study may be waived if the physicochemical, structural and in vitro biological analyses, combined with human pharmacokinetic studies and pharmacodynamic markers reflecting the pharmacological effect and concentration of the active substance, can provide strong evidence for biosimilar comparability. (3) If the evidence for clinical biosimilarity is to be derived from pharmacokinetic studies supported by studies conducted with non-surrogate pharmacodynamic/biomarkers, it is recommended that this (fingerprinting) approach be discussed with the Agency. In such cases, the study plan should include the clinical justifications, together with a proposal on the width of the equivalence margins, as well as the criteria for demonstrating a comparable safety profile.

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Efficacy Studies

ARTICLE 21 - (1) If efficacy studies are considered necessary, preferably double-blind, randomised, parallel clinical trials should be conducted to clinically compare the biosimilar medicinal product with the reference medicinal product, together with efficacy endpoints. The study design of the clinical trial planned to be conducted by the applicant may be submitted to the Agency for consultation. (2) The study population should generally be sensitive enough to reveal potential differences between the biosimilar and the reference medicinal product and should reflect the approved therapeutic indications of the reference product. From time to time, changes in clinical practice (for example, concomitant medicinal products used in a combination therapy, treatment line, or severity of the disease) may necessitate deviations from the approved therapeutic indication. Such deviations must be submitted with justification. a) Study Designs

I- In general, an equivalence design should be used. Where scientifically justified, taking into account the properties of the reference medicinal product (for example, the safety profile/tolerability, dose range and dose-response relationship of the reference medicinal product), a non-inferiority study design may be acceptable. II- A non-inferiority study design is acceptable only in cases where the possibility of a clinically valid and meaningful increase in efficacy can be excluded on a scientific and mechanistic basis. However, as with equivalence studies, assay sensitivity should be taken into consideration. III- If the use of a non-inferiority study design is being considered, it is recommended that it be discussed with the Agency. b) Efficacy Endpoints I- The aim of efficacy studies should be to confirm the comparable clinical performance of the biosimilar and the reference medicinal product, rather than to demonstrate the already established efficacy of the reference medicinal product. II- In efficacy studies, comparability should be demonstrated in clinical models and study conditions of sufficient sensitivity. The applicant should justify that the selected model is appropriate and sensitive to detect potential differences relating to efficacy and safety. If there are deviations from the endpoints recommended in disease-specific published guidelines, they should be scientifically justified. III- Differences observed between the efficacy of the biosimilar and the reference medicinal product in efficacy studies should be discussed in terms of their clinical relevance. In general, the purpose of the clinical data is to address the small differences observed in previous steps and to confirm the comparable clinical performance of the biosimilar and the reference medicinal product. Clinical data cannot be used to justify significant differences in quality attributes. IV- The correlation between the stringent primary clinical endpoints recommended by guidelines for products containing new active substances and other clinical/pharmacodynamic endpoints that are more sensitive in detecting clinically meaningful differences may have been demonstrated in previous clinical studies conducted with the reference medicinal product. In this case, there is no obligation to use the same primary efficacy endpoints as those used in the marketing authorisation application of the reference medicinal product. Nevertheless, to facilitate comparisons, it may be recommended to include some common endpoints (for example, secondary endpoints) from the clinical studies conducted with the reference medicinal product. V- Comparability margins in efficacy studies should be pre-specified and justified on statistical and clinical grounds using data from the reference medicinal product. As with all comparative clinical trial designs, assay sensitivity should also be taken into consideration.

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Clinical Safety

ARTICLE 22 - (1) Clinical safety is of importance throughout the entire clinical development programme and is obtained during the initial pharmacokinetic and/or pharmacodynamic assessments and as part of the pivotal clinical efficacy trial. (2) The amount of comparative safety data to be obtained should be determined depending on the type and severity of the safety concerns known for the reference medicinal product and should be collected prior to authorisation. The duration of pre-authorisation safety follow-up should be justified. (3) Attention should be paid to comparing the adverse reactions of the biosimilar and the reference medicinal product in terms of type, severity and frequency, in particular those described in the Summary of Product Characteristics of the reference medicinal product. (4) The applicant should present in the application dossier an assessment of the specific risks anticipated for the biosimilar medicinal product. This assessment includes a description of the potential safety concerns that may arise from a manufacturing process different from that of the reference medicinal product, in particular risks related to infusion-related reactions and immunogenicity. (5) The immunogenicity potential of the biosimilar medicinal product should be investigated in comparison with the reference medicinal product. Unless a deviation from this approach can be justified, the principles set out in the relevant current guidelines should be followed. The type and amount of immunogenicity data will depend on the experience gained with the reference medicinal product and the product class. (6) Immunogenicity testing of the biosimilar and/or reference medicinal product should be performed within the biosimilar comparability studies using the same assay format and sampling schedule, in accordance with valid standards. The analytical methods should be capable of detecting at least all antibodies developing against the biosimilar molecule, preferably antibodies developing against both the reference medicinal product and the biosimilar medicinal product.

(7) In comparative immunogenicity studies, a sufficient number of patients should be treated for an acceptable duration. In each study arm (biosimilar and reference), the incidence and severity of antibody responses against the product, the kinetics of antibody development and persistence in the systemic circulation, and the effects of antibody development on safety, efficacy and pharmacokinetics should be assessed. In the selection of the study population, factors such as the immunocompetence status of the patients, immunosuppressive medicinal products taken previously or being taken during the study, and historical literature data on the immunogenicity of the reference medicinal product should be taken into consideration. (8) Comparative immunogenicity testing should be performed using a tiered approach and should include screening tests, confirmatory assays and appropriate assays to determine whether binding antibodies are neutralising. In parallel to these tests, independent binding antibody assays should be developed in which the biosimilar or the reference medicinal product is included as the capture ligand in the test. Each assay should be validated and shown to be capable of sensitively detecting antibodies in the presence of the product. In blood samples taken from both treatment arms, the cross-reactivity of antibodies that may develop against the biosimilar and the reference medicinal product should be appropriately examined. Any deviation from this approach should be justified. Furthermore, in patient samples found positive for binding antibodies by confirmatory binding tests, the capacity of these antibodies to neutralise the product should be tested, and if this is not done, it should be justified. In the selection of an appropriate format for the neutralising antibody test, the mechanism of action of the product should be taken into consideration; for this purpose, depending on the mechanism of action, a competitive ligand-binding assay or a cell-based assay may be appropriate. (9) The duration of the immunogenicity study should be justified on a case-by-case basis depending on the duration of treatment, the clearance of the product from the circulation (in order to avoid interference from the antigen) and the onset time of the humoral immune response (for example, at least 4 weeks when any immunosuppressive agent is used). The follow-up duration should be justified based on the course and characteristics of the unwanted immune responses described for the reference medicinal product (for example, a low clinically meaningful immunogenicity risk or the absence of a significant immunogenicity trend increasing

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over time). In the case of chronic administration, one year of follow-up data are generally required prior to authorisation. Shorter (but at least 6 months) follow-up data prior to authorisation may be justified based on the immunogenicity profile of the reference medicinal product. If needed (particularly if 6-month follow-up data are available prior to authorisation), immunogenicity data may be submitted post-authorisation for an additional period of up to one year. In this case, product-specific biosimilar guidelines, if available, may be referred to. (10) Increased immunogenicity compared to the reference medicinal product may pose a problem in terms of the benefit/risk analysis and may call the biosimilarity into question. On the other hand, lower immunogenicity is not an obstacle to being accepted as a biosimilar medicinal product. A lower level of neutralising antibodies developing against the biosimilar medicinal product does not mean that the biosimilar product is more effective than the reference medicinal product for the entire study population. Therefore, it is recommended that an additional analysis of efficacy and safety be performed for the subgroup of patients who do not develop antibodies during the study. This subgroup analysis may be useful for determining that, in principle, the efficacy of the biosimilar and the reference medicinal product is similar, provided that they are not affected by an immune response.

Extrapolation of Efficacy and Safety from One Therapeutic Indication to Another Therapeutic Indication

ARTICLE 23 – (1) The reference medicinal product may have more than one therapeutic indication. Where biosimilar comparability has been demonstrated in one indication, extrapolation of the clinical data to the other indications of the reference product may be acceptable, provided that it is scientifically justified. Requests for extrapolation will be assessed on a product basis, taking into account the totality of quality, non-clinical and clinical data.

(2) In cases where biosimilar comparability has been demonstrated through detailed physicochemical and structural analyses, supplemented by in vitro functional tests and clinical data in one therapeutic indication (efficacy and safety and/or pharmacokinetic/pharmacodynamic data), extrapolation of safety and efficacy to other indications may be expected. For each indication for which extrapolation is requested, a scientific justification must be submitted, prepared by taking into consideration the mechanisms of action of the product, its safety profile, the dosage regimen, the existing clinical experience with the reference medicinal product, and the relevant pathophysiological mechanisms applicable to the indication concerned. In addition, the extrapolation of immunogenicity from the studied indication/route of administration to the other indications/routes of administration must also be justified. Additional data are required in the following cases:

a) If the active substance of the reference medicinal product interacts with more than one receptor having different effects in the tested and untested therapeutic indications.

b) If the active substance itself has more than one active site and these active sites have different effects in different indications.

c) If the indication in which similarity has been demonstrated is not representative of the other indications in terms of efficacy or safety (for example, if the studied indication is not sufficiently sensitive to determine efficacy and safety differences across all indications of the biological medicinal product).

(3) Immunogenicity depends on multiple factors (for example, concomitantly administered medicinal products, the type of disease, immune status, etc.), including the route of administration, dosing regimen, patient- and disease-related factors. There may be differences between the studied indication and the indications for which extrapolation is requested with regard to immunogenicity.

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Pharmacovigilance

ARTICLE 24 – (1) Data obtained from pre-authorisation clinical trials are generally insufficient to identify rare adverse effects. For this reason, the clinical safety of biosimilar medicinal products must be monitored closely and continuously in the post-authorisation phase, including an ongoing benefit/risk assessment.

(2) Within the framework of the authorisation procedure, the applicant must submit a description of the pharmacovigilance system and a risk management plan, in accordance with the current relevant guidelines. The risk management plan must take into consideration the identified and potential risks associated with the use of the reference medicinal product, and must detail how these matters will be addressed during the post-marketing follow-up period. Immunogenicity must be specifically addressed in this context.

(3) Any safety follow-up specific to the reference medicinal product or product class must be adequately addressed in the pharmacovigilance plan of the biosimilar medicinal product. Applicants are encouraged to participate in existing pharmacoepidemiological studies for the reference medicinal product. However, the initiation of new studies may be necessary. In principle, the risk minimisation activities implemented for the reference medicinal product should also be incorporated into the risk management programme of the biosimilar medicinal product. Any deviation from this situation (for example, if the risk minimisation is related to a device used in conjunction with the reference medicinal product) must be justified.

(4) For suspected adverse reactions related to biological medicinal products, the unambiguous identification of the product concerned in terms of manufacturing is of particular importance. For this reason, all appropriate measures must be taken to clearly identify, by trade name and batch number, any biological medicinal product that is the subject of a suspected adverse reaction report.

Related Guidelines

ARTICLE 25 – Other national and international guidelines addressing quality, non-clinical and clinical issues must also be taken into consideration during the development of biosimilar medicinal products.

Entry into Force

ARTICLE 26 – (1) This Guideline enters into force upon approval by the President of the Agency.

(2) The provisions of the Guideline containing references to requesting/consulting the Agency within the scope of obtaining scientific advice prior to submission shall enter into force following the publication by the Agency of the legislation on the subject concerned, while the other provisions of the Guideline shall enter into force on the date of publication of this Guideline.

Execution

ARTICLE 27 – (1) The provisions of this Guideline shall be executed by the President of the Turkish Medicines and Medical Devices Agency (TİTCK).

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