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GUIDELINE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE OF HUMAN MEDICINAL PRODUCTS İRD-KLVZ-11

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Objective:

ARTICLE 1- (1) The objective of this guideline is to establish the procedures and principles for bioavailability and bioequivalence studies submitted at the licensing stage and thereafter of human medicinal products.

Scope:

ARTICLE 2- (1) This guideline covers; a) All evaluations, including the design and conduct of bioavailability and bioequivalence studies of human medicinal products, b) Comparative bioavailability studies in which different formulations used during the development of a human medicinal product containing a new chemical active substance or substances are evaluated, c) The procedures and principles relating to comparative bioavailability studies (relative bioavailability studies) in which applications for different dosage forms that do not rely solely on bioequivalence data are evaluated. (2) Comparative studies of biological/biotechnological medicinal products with reference medicinal products fall within the scope of this guideline, and the provisions of this guideline apply in addition to the provisions of the Guideline on Biosimilar Medicinal Products for biosimilar medicinal products.

Legal Basis:

ARTICLE 3- (1) This guideline has been prepared on the basis of the Regulation on the Licensing of Human Medicinal Products, which entered into force upon its publication in the Official Gazette No. 31686 dated 11/12/2021.

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Definitions and Abbreviations:

ARTICLE 4- (1) In this Guideline; a) Relative bioavailability: the bioavailability ratioed to the bioavailability obtained by administration via a route allowing the highest bioavailability other than intravenous use, or by a pharmaceutical form administered via the same route but providing higher bioavailability (e.g., tablet versus oral solution), b) Human medicinal product: 1) Any substance or combination of substances presented as having properties for treating or preventing disease in humans, or 2) Any substance or combination of substances that may be used in or administered to humans with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis, c) Content of the human medicinal product: the quantitative amount of the active substance or substances contained in each dosage unit, unit volume or unit weight of the human medicinal product, depending on the pharmaceutical form, d) Bioequivalence: the state in which the bioavailability (rate and extent) of two human medicinal products containing the same active substance, which are pharmaceutically equivalent or are pharmaceutical alternatives of each other, following administration at the same molar dose via the same route of administration, falls within pre-established acceptable limits, e) Batch: the batches used in in vivo studies, f) Bioavailability: the rate and extent to which the active substance or the fraction responsible for the therapeutic effect is absorbed from the pharmaceutical form and enters the systemic circulation, and thus becomes present at the site of action in the body or in biological fluids reflecting it (usually serum or plasma), g) Equivalent medicinal product: a medicinal product having the same qualitative and quantitative composition in terms of the active substance(s) as the reference medicinal product and the same pharmaceutical form, whose bioequivalence has been demonstrated by appropriate bioavailability studies (Different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in their properties with regard to safety or efficacy. In such cases, additional information shall be submitted by the applicant to demonstrate the safety or efficacy of the different salts, esters or derivatives of the licensed active substance(s). Various immediate-release oral pharmaceutical forms are regarded as one and the same pharmaceutical form. Where the applicant fulfils the relevant criteria set out in detail in the guidelines relating to the equivalent medicinal product, there is no need to submit bioavailability studies.), h) Hybrid application: a licensing application based partly on data of the reference product and partly on data obtained from studies on the new product, i) Hybrid product: the human medicinal product that is the subject of a hybrid application, j) Summary of Product Characteristics (SmPC): the written information prepared for healthcare professionals regarding the human medicinal product, k) Agency: the Turkish Medicines and Medical Devices Agency (TİTCK), l) Absolute bioavailability: the bioavailability ratioed to the bioavailability measured following intravenous administration of the same molar amount of the medicinal product, m) Reference medicinal product: the human medicinal product licensed and placed on the market by our country, the ICH founding or permanent regulatory authorities, or the regulatory authorities of the United Kingdom or Australia, with a full dossier, for the purpose of first marketing in the world, n) Reference product: the human medicinal product accepted as the reference against which the test product will be compared in comparative bioavailability and bioequivalence studies,

o) Test product: the product against which the reference product will be compared in comparative bioavailability and bioequivalence studies, are meant. General Principles: Bioequivalence studies

ARTICLE 5- (1) The number and design of the studies depend on the physicochemical characteristics of the active substance, its pharmacokinetic properties and the proportionality in the composition, and shall be justified accordingly. (2) By means of bioequivalence studies, the biopharmaceutical similarity between the reference product and the equivalent medicinal product is evaluated by establishing a link with the data obtained from preclinical tests and clinical trials relating to the reference product. (3) For bioavailability/bioequivalence studies submitted to the

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Agency for evaluation, it is mandatory to submit to the Agency a good clinical practice (GCP) certificate issued by the Agency, the ICH founding or permanent member countries, or the regulatory authorities of the United Kingdom or Australia, or a GCP certificate issued by independent organisations authorised by these authorities (the certificate of authorisation must be submitted in the dossier). The validity of GCP certificates shall be considered to be 2 years, unless otherwise specified in the certificate or in cases where the validity period is not specified in the certificate. In cases where it is demonstrated that the GCP certificate cannot be submitted, an inspection report issued by the relevant regulatory authority or the authorised independent organisation must be submitted. The study date may cover a period of at most 2 years from the date of issue of the inspection report. (4) The applicant is responsible for the currency of the GCP certificates, and it is mandatory to notify the Agency of any relevant changes. Design of the study

ARTICLE 6- (1) The study shall be designed in such a way that the formulation effect can be distinguished from other effects. a) Standard design If two formulations are being compared, a randomized, two-period, two-sequence, single-dose crossover design is recommended. In these designs, at the beginning of the second period, the drug concentration in all participants (volunteers) must be below the bioanalytical limit of quantification. To ensure this, under normal conditions, the administration periods shall normally be separated by a washout period of at least 5 elimination half-lives. b) Alternative designs

Provided that the study design and statistical analyses remain scientifically valid, well-known alternative designs may be applied under certain conditions. For example: 1) A "parallel design" for substances with a very long half-life, 2) A "replicate design" for substances whose pharmacokinetic parameters exhibit high variability, 3) A "multiple-dose study in patients" in cases where a single-dose study cannot be conducted in healthy volunteers due to tolerability issues and a single-dose study is not appropriate in patients, 4) A "multiple-dose study" in cases where, due to problems arising from the sensitivity of the analytical method, plasma concentrations cannot be accurately measured after single-dose administration, but steady-state concentrations (following multiple-dose administration) can be reliably measured. (2) A multiple-dose study is less sensitive in detecting differences in Cmax values. Therefore, multiple-dose administration is performed only in cases where it is justified that the sensitivity of the analytical method cannot be improved in a single-dose administration and that the parent compound cannot be measured despite a single-dose administration exceeding the therapeutic dose (with no safety and tolerability concerns). (3) In light of recent developments in bioanalytical methods, the inability to measure the parent drug with high accuracy and precision is not considered a usual situation. Therefore, a multiple-dose study instead of a single-dose study, depending on the sensitivity of the analytical method, is accepted only in exceptional cases. (4) In steady-state studies, the washout period of the first administration may overlap with the time to reach steady state of the second administration, provided that a period of at least 5 times the terminal half-life elapses for the second administration to reach steady state.

Reference and test products

ARTICLE 7- (1) Care shall be taken to ensure that the reference and test products have manufacturing dates that are as close as possible to each other. (2) In bioavailability and bioequivalence studies;

a) The reference medicinal product obtained, which has been authorized and placed on the market in our country, in any of the ICH founding or permanent member countries, in the United Kingdom, or in Australia1, b) In cases where no reference medicinal product complying with the provisions set forth in subparagraph (a) of this paragraph is available; provided that this situation is demonstrated with supporting documents and the rationale for preferring the product to be selected is submitted with supporting documents, the product proposed as a reference obtained from the countries specified in the same subparagraph, after approval by the Agency, c) Limited to medicinal products for human use in the treatment of rare diseases, in cases where the reference

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medicinal product cannot be obtained from the countries specified in subparagraph (a), the reference medicinal product obtained from a country deemed appropriate in the assessment conducted by the Agency prior to the marketing authorization application may be used as the reference product. (3) It shall be demonstrated by the applicant that the test product used in the study represents the product to be placed on the market. For example, for an oral solid dosage form with systemic action, the test product: a. Shall generally, and unless otherwise justified, be taken from a batch corresponding to at least 1/10 of the production scale or consisting of at least 100,000 units (whichever is greater). b. The manufacture of the batches used shall provide a high level of assurance that the product and process can be manufactured on an industrial scale. In the case of a production batch smaller than 100,000 units, a full production batch is required. c. The specification and characterization of the critical quality attributes of the finished product, such as dissolution, shall be demonstrated with the test batch used in the clinical study in which bioequivalence has been proven. d. Product samples taken from additional pilot or full-scale production batches submitted to support the application shall be compared with samples taken from the test batch used in the bioequivalence study and shall exhibit similar in vitro dissolution profiles when appropriate dissolution test conditions are applied (see Annex-2). (4) Comparative dissolution profile tests shall be performed between the batches used in the in vivo study and shall be submitted during the marketing authorization application. (5) For other immediate-release pharmaceutical forms with systemic action, the justification of the representative nature of the test batch shall be carried out in a similar manner. (6) The reference and test products shall be packaged, before being shipped to the site where the study will be conducted or at the study site, for each participant (volunteer) and period, separately, preserving the inner packaging, for the packaging types available (such as blister, single-dose packaging types), and labeled separately.

1 In cases where the clinical studies conducted during the development of the reference product were performed in a different population (Caucasian race, etc.), data or information shall be submitted demonstrating that the difference in question will not cause a scientifically significant change in terms of pharmacodynamics and pharmacokinetics.

Packaging, including labeling, shall be carried out in accordance with good manufacturing practices. Where the sites located abroad are requested by the Agency, documentation demonstrating that they possess standards equivalent to good manufacturing practice requirements shall be submitted. (7) It shall be possible to clearly identify the identity of the product administered to each participant (volunteer) in each study period. The packaging, labeling, and administration of the products to the participants (volunteers) shall be documented in detail. This documentation shall include all measures necessary to prevent and identify potential dosing errors. The use of labels with a tear-off portion is recommended.

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Participants (Volunteers)

ARTICLE 8- (1) The number of volunteers to be enrolled in the study should be determined according to an appropriate sample size calculation. In a bioequivalence study, the number of evaluable volunteers should not be less than 12. (2) The volunteer population to be used in bioequivalence studies should be selected with the aim of enabling the detection of differences between pharmaceutical products. In order to reduce variability not related to differences between products, studies should be conducted in healthy volunteers, provided that this is not unethical in terms of drug safety. (3) The inclusion of healthy volunteers in studies is considered sufficient to determine formulation differences and to allow the extrapolation of the results to populations in which the reference product is used (elderly, children, patients with hepatic or renal impairment, etc.). (4) Inclusion and exclusion criteria should be clearly specified in the protocol. Volunteers should be 18 years of age or older and should preferably have a Body Mass Index of 18.5-30 kg/m2. (5) Volunteers should be screened for suitability for the study by means of clinical laboratory tests, medical history and physical examination. Depending on the therapeutic class and safety profile of the drug, special medical examinations and precautions may be required before, during and after the completion of the study. Volunteers may be of both sexes; however, the risks for women of childbearing potential should be taken into consideration. Volunteers should preferably be non-smokers and should not have a history of alcohol or drug abuse. Scientific data on the effect of phenotype and/or genotype differences on the pharmacokinetics and safety of the active substance should be submitted in the study. (6) The groups in parallel design studies should be comparable with respect to variables known to affect the pharmacokinetics of the active substance (e.g., age, body weight, sex, ethnic origin, smoking status, rapid/slow metabolism). This is a fundamental prerequisite for the validity of the results obtained from the studies. (7) If the active substance under investigation is known to have adverse effects and its pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to enroll patients in the study under appropriate precautions and supervision.

Conduct of the Study

ARTICLE 9- (1) Test conditions should be standardised in order to minimise the variability of all factors not related to the test product. Therefore, standardisation of diet, fluid intake and exercise is recommended. The time of day when the drug is to be administered should be specified. Unless otherwise specified, the volunteers should be fasted for at least 8 hours prior to administration of the products. Since fluid intake may influence gastric emptying for oral dosage forms, the test and reference products should be administered with a standard volume of water (at least 150 mL). It is recommended that water be permitted ad libitum except for the 1 hour before and after drug administration, and that no food be allowed for at least 4 hours post-dose. Standardised meals should be provided after an appropriate interval of time following dosing (e.g. 12 hours), with the content and timing of the meals standardised.

(2) In studies to be conducted under fed conditions, the timing relationship between administration of the test and reference products and food intake should be set according to the Summary of Product Characteristics (SmPC) of the reference product. If there is no specific instruction in the reference SmPC, it is recommended that volunteers start their meal 30 minutes before product administration and finish it within 30 minutes.

(3) Since the bioavailability of the therapeutically active moiety from a dosage form may be dependent upon the transit time in the gastro-intestinal tract and regional blood flow, standardisation of posture and physical activity may be necessary.

(4) The volunteers should refrain from any food and drink that may interact with the circulatory, digestive, hepatic and renal systems (e.g. alcoholic beverages or specific fruit juices such as grapefruit juice) for an adequate period of time before and during the study. Volunteers should not take any drug (including herbal medicinal products) for an appropriate interval of time before and during the study. However, the use of contraceptives is permitted. In cases where

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concomitant medication is unavoidable, if a volunteer takes other drugs (e.g. to treat adverse events such as headache), the concomitant medication should be reported (including the dose administered and the time/duration of administration), and, if possible, the active substances recommended for use from among the pharmacological classes with a high likelihood of concomitant use should be specified in the protocol, and any potential effects on the results obtained from the study should be addressed. In cases where concomitant medication is required for all volunteers due to safety or tolerability reasons (e.g. opioid antagonists, antiemetics), any likely interaction or risk of bioanalytical interference that may affect the study results should be addressed.

(5) Products for which the reference product SmPC explicitly states that they are to be used in combination with another product (e.g. certain protease inhibitors used in combination with ritonavir) may be investigated either in the approved combination or without concomitant administration of the recommended product.

(6) In bioequivalence studies with endogenous substances, the factors that may influence the baseline (endogenous) levels of the endogenous substance should, if possible, be controlled (e.g. strict control of dietary intake).

(7) A sufficient number of samples should be collected to describe the plasma concentration-time profile. The sampling schedule should include frequent sampling around the expected tmax in order to obtain a reliable estimate of Cmax. In particular, sampling should be planned in such a way as to avoid the possibility that the Cmax value is the first point of the concentration-time curve. In addition, the sampling schedule should cover a plasma concentration-time curve long enough to allow for a reliable estimate of the extent of exposure, meaning that a situation is reached in which AUC(0-t) covers at least 80% of AUC(0-∞). In order to obtain a reliable estimate of the terminal rate constant (necessary for a reliable estimate of the AUC(0-∞) value), at least three or four samples should be taken over the terminal log-linear phase.

(8) A truncated AUC at 72 hours, i.e. AUC(0-72), may be used as an alternative to AUC(0-t) for comparison of the extent of exposure for immediate-release formulations, since the absorption phase is completed within the 72-hour period. Therefore, for any immediate-release formulation, it is accepted that a sampling duration of longer than 72 hours is not required, irrespective of the half-life of the drug.

(9) In multiple-dose studies, for an accurate and precise determination of AUC(0-τ), a sample should be taken immediately before dosing (within 5 minutes), and it is recommended that the last sample be taken within 10 minutes of the nominal duration of the dosing interval.

(10) If the biological matrix is urine, urine should normally be collected for a period of at least three times the terminal elimination half-life. However, in line with the advice regarding plasma sampling, there is no need to collect urine for longer than 72 hours. If the excretion rate is to be determined, the collection intervals during the absorption phase should be kept as short as possible.

(11) For endogenous substances, the sampling schedule should allow for characterisation of the baseline profile of the endogenous substance for each volunteer in each period. The baseline level is usually determined from 2-3 samples taken before administration of the products. In cases where fluctuations in the endogenous baseline level due to circadian rhythms need to be taken into account, samples may need to be taken at regular intervals during the 1-2 days prior to administration.

(12) A bioequivalence study should generally be conducted under fasting conditions. Fasting conditions are considered the most sensitive condition for detecting the potential difference between formulations. If the reference product is recommended in its SmPC to be taken either fasting or irrespective of food intake, the bioequivalence study should be conducted under fasting conditions. If the reference product is recommended in its SmPC to be taken only in the fed state, the bioequivalence study should generally be conducted under fed conditions. However, bioequivalence studies for products with specific formulation characteristics (e.g. microemulsions,

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solid dispersions) should be conducted under both fasting and fed conditions if the product is not required to be taken only fasting or only fed.

(13) In cases where information on both fasting and fed conditions needs to be obtained, a bioequivalence study may be conducted using either two separate, two-way crossover designs or a four-way crossover design.

(14) In studies conducted under fed conditions, the composition of the meal should be set according to the SmPC of the reference product. If there is no specific recommendation in the reference product SmPC, the meal should be high-fat (approximately 50% of total calories) and high-calorie (approximately 800-1000 kcal). The protein, carbohydrate and fat content of the meal should be specified (in grams, calories and relative caloric content (%)). The protein, carbohydrate and fat calories of the meal should be approximately 150, 250 and 500-600 kcal, respectively.

Characteristics to be investigated

ARTICLE 10- (1) The actual time of sampling shall be used in the estimation of pharmacokinetic parameters. In single-dose bioequivalence studies, AUC(0-t), AUC(0-∞), residual area, Cmax and tmax values shall be determined. In studies with a 72-hour sampling period where the concentration at 72 hours is measurable, it is not necessary to report AUC(0-∞) and the residual area; it is sufficient to report the AUC(0-72h) value. Additional parameters such as the terminal rate constant (λz) and t1/2 may be reported.

(2) In steady-state studies, for immediate-release formulations, AUC(0-τ), Cmax,ss, and tmax,ss values shall be determined in order to assess bioequivalence.

(3) When urinary data are used, Ae(0-t) and, where applicable, Rmax values shall be determined.

(4) Compartment models shall not be used for the determination of pharmacokinetic parameters in bioequivalence studies.

(5) In principle, the assessment of bioequivalence studies should be based on the measured concentrations of the parent compound. The reason for this is that, in detecting differences between formulations, the Cmax of the parent compound is generally more sensitive than the Cmax of the metabolite with respect to the rate of absorption.

(6) For inactive prodrugs, demonstration of bioequivalence for the parent compound is also recommended. It is not necessary to measure active metabolites. However, for some prodrugs, difficulties may arise in demonstrating bioequivalence for the parent compound due to low plasma concentrations and rapid elimination. In such cases, demonstrating bioequivalence for the main active metabolite without measuring the parent compound is acceptable. Within the scope of this guideline, a compound may be considered an inactive prodrug if the contribution of the parent compound to clinical efficacy is very low or absent.

(7) The use of a metabolite instead of the active parent compound is not recommended. This may be considered only if the applicant can justify that a reliable measurement of the parent compound cannot be obtained after single-dose administration, that the sensitivity of the analytical method for the measurement of the parent compound cannot be improved, and also taking into account the option of using a higher single dose in the bioequivalence study. In the light of recent developments in bioanalytical methods, since the inability to measure the parent compound with high accuracy and precision is not a common situation, the use of a metabolite instead of the active parent compound is acceptable only in exceptional circumstances. When metabolite data are used instead of active parent compound concentrations, the applicant should submit supportive data demonstrating that the metabolite exposure reflects the parent compound and that the formation of the metabolite is not saturated at therapeutic doses.

(8) The use of achiral bioanalytical methods is generally acceptable. However, each enantiomer shall be measured when all of the following conditions are met: 1) If the enantiomers exhibit different pharmacokinetic properties, 2) If the enantiomers exhibit a marked difference in pharmacodynamic terms, 3) If the exposure (AUC) ratio of the enantiomers changes due to

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differences in absorption rate. In the presence of the above conditions, or if this is unknown, each enantiomer shall be measured. If one enantiomer is pharmacologically active and the other enantiomer is inactive or has a low contribution to activity, it is sufficient to demonstrate bioequivalence for the active enantiomer only.

(9) In cases where a reliable measurement of the plasma concentration-time profile of the parent compound is not possible, urinary excretion data may be used to determine the extent of exposure to the drug. However, when urinary data are used to determine peak exposure, the reason for choosing this approach shall be justified. If a reliable plasma Cmax value can be determined, this value shall be combined with urinary data on the extent of exposure for the assessment of bioequivalence. When urinary data are used, the applicant should submit all available data supporting that urinary excretion reflects plasma exposure.

(10) If the substance under investigation is an endogenous substance, pharmacokinetic parameters shall be calculated using baseline correction. Thus, the calculated pharmacokinetic parameters can reflect the additional concentrations resulting from the administration. Provided that the dose is well tolerated, doses above the therapeutic dose may be used in bioequivalence studies of endogenous drugs. As a result of this practice, the additional concentrations above the baseline can be reliably determined. If it has not been previously established that there is a difference in exposure following administration of different doses of an endogenous substance, the difference in exposure between different doses shall be demonstrated by means of a pilot study or as part of a bioequivalence study using different doses of the reference formulation, in order to ensure that the dose used for the bioequivalence comparison is sufficiently sensitive to reveal potential differences between formulations. The method to be used for baseline correction shall be pre-specified and justified in the study protocol. In general, a standard subtraction method is preferred in which either the mean of individual pre-dose endogenous concentrations or the individual pre-dose endogenous AUC is subtracted. In rare cases where significant increases over the baseline of endogenous substances are observed, baseline correction may not be required. In bioequivalence studies conducted with endogenous substances, at the beginning of the second period, the amount of drug that may result from the administration in the first period (carry-over effect) cannot be directly determined; therefore, care shall be taken to ensure that the washout period is of sufficient length.

Loss to be evaluated

ARTICLE 11- (1) Where an application is made for more than one strength of a test product, depending on the proportionality of composition between the different strengths and on the matters specified below, it may be sufficient to determine bioequivalence for only one or two strengths. The strength(s) to be investigated shall be determined based on the linearity of the pharmacokinetics of the active substance.

(2) In cases where pharmacokinetics is non-linear (cases in which a proportional increase in AUC is not observed with increasing dose), there may be a difference between individual strengths in terms of sensitivity for detecting potential differences between formulations.

(3) Within the scope of this guideline; when the strength investigated (or the strength in the planned bioequivalence study) is compared with the strength for which a waiver is considered, pharmacokinetics is considered linear if the difference in dose-adjusted mean AUC values does not exceed 25%.

(4) The applicant should evaluate all available data with respect to dose proportionality in order to assess linearity.

(5) If bioequivalence has been demonstrated using the strength(s) that are the most sensitive for detecting a potential difference between products, in vivo bioequivalence studies with the other strength(s) are not required.

(6) Where a waiver applies for additional strengths, the following general conditions shall be fulfilled:

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1) The pharmaceutical products shall be manufactured using the same manufacturing process,

2) The composition of the different strengths shall be qualitatively the same,

3) The composition of the strengths shall be quantitatively proportional, i.e. the ratio of the amount of each of the major excipients (excipients other than coating components, empty capsule, colouring agents and flavourings in immediate-release products) to the amount of the active substance(s) shall be the same for all strengths.

When evaluating the waiver situation, even if there is some deviation from quantitatively proportional composition in the strengths investigated, condition 3 shall be considered fulfilled if the following conditions i) and ii), or i) and iii) are satisfied for the strength used in the bioequivalence study and the strengths for which a waiver is considered:

i. If the amount of the active substance(s) is less than 5% of the tablet core weight or the capsule content weight,

ii. If the amounts of the major excipients in the core or in the capsule content are the same for the relevant strengths and only the amount of the active substance varies,

iii. If the amount of the filler varies in relation to the amount of the active substance, while the amounts of the other excipients and the capsule content are the same for the relevant strengths.

4) Suitable in vitro dissolution data shall support the waiver of in vivo bioequivalence testing.

(7) For products with linear pharmacokinetics meeting all of the conditions 1) to 4) above, demonstrating bioequivalence with only a single strength is sufficient. In cases where linear pharmacokinetics is observed and the active substance is highly soluble (see Annex-4), selecting a lower strength instead of the highest strength may also be acceptable. Furthermore, if the highest strength cannot be administered to healthy volunteers due to safety/tolerability concerns, a lower strength may be selected. In addition, if, following single-dose administration of the highest strength, plasma concentration measurements with an adequate level of precision cannot be performed due to a sensitivity problem of the analytical method, a higher dose may be selected (preferably a dose obtained by using more than one tablet of the highest strength). Provided that it is well tolerated in healthy volunteers and there is no absorption or solubility limitation at a single dose, the selected dose may be higher than the highest therapeutic dose.

(8) With increasing dose within the therapeutic dose range:

a) For drugs with non-linear pharmacokinetics characterized by a greater than proportional increase in AUC, the bioequivalence study should generally be conducted at the highest strength. In addition, if the highest strength cannot be administered to healthy volunteers due to safety/tolerability concerns, a lower strength may be selected. Furthermore, in accordance with the advice given above for products with linear pharmacokinetics, a higher dose may be used in case of sensitivity problems with the analytical method.

b) For drugs with non-linear pharmacokinetics characterized by a less than proportional increase in AUC, bioequivalence should generally be demonstrated at both the highest and the lowest strength (or a strength within the linear range), in which case two bioequivalence studies are required. If the non-linear pharmacokinetics results not from limited solubility but, for example, from causes such as saturation of transport proteins, then, in addition to fulfilling all of the conditions 1 to 4 mentioned above and provided that neither the test nor the reference product contains any excipient that may affect gastrointestinal motility or transport proteins, it is sufficient to demonstrate bioequivalence at the lowest strength (or a strength within the linear range).

(9) In cases where there are analytical sensitivity problems that may prevent a study from being conducted at the lowest strength, or safety or tolerability problems at the highest strength in healthy volunteers, other strengths may be selected.

(10) In cases where the bioequivalence assessment needs to be performed with more than two strengths (e.g. where there is a deviation from proportional composition), a bracketing

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approach may be used.

In this case, if the selected strengths represent the extreme strengths (e.g. the highest and the lowest strengths, or the two strengths showing the greatest difference in terms of composition), two bioequivalence studies may be considered sufficient.

(11) In cases where, due to non-linear absorption or a deviation from proportional composition, the bioequivalence assessment needs to be performed with two strengths and the study needs to be conducted under both fasted and fed conditions, it may be sufficient to study one of the strengths under both fasted and fed conditions. The waiver of either the fasted or the fed condition for the other strength(s) should be based on previous information and/or pharmacokinetic data obtained from the study conducted with the strength tested under both fasted and fed conditions. The condition (fasted or fed) selected for testing the other strengths should be the most sensitive condition for detecting differences between the products.

(12) The conditions relating to proportional composition shall be fulfilled for all active substances in fixed combinations. When evaluating the amount of each of the active substances in a fixed combination, the other active substance(s) may be considered as excipients. In bilayer tablets, each layer may be evaluated independently of the other.

Bioanalytical method

ARTICLE 12- (1) The bioanalytical part of bioequivalence studies shall be conducted in accordance with the principles of Good Laboratory Practice (GLP). However, since human bioanalytical studies fall within the scope of Good Clinical Practice (GCP), there is no need for the facilities where these studies are conducted to be additionally monitored as part of a GLP compliance programme. (2) The bioanalytical methods used shall be well characterised, validated and documented. An in-study validation shall be performed in each analytical run using quality control samples. (3) The principal characteristics required for the bioanalytical method in order to guarantee acceptable performance and reliable analytical results are as follows: selectivity, lower limit of quantification, response function (performance of the calibration curve), accuracy, precision, stability, dilution integrity, carry-over and matrix effect. (4) Since the pre-dose concentration must not exceed 5% of the Cmax value, the lower limit of quantification shall be 1/20 of the Cmax value or lower. (5) The reanalysis of study samples shall be pre-specified and defined in the study protocol (and/or SOP) before the analysis of the samples actually begins. Under normal circumstances, reanalysis of subject samples for a pharmacokinetic reason is not generally considered an acceptable practice. This is of particular importance for bioequivalence studies, as it may cause bias in the study results. (6) The analysis of samples shall be performed without taking into account the information and data on dosing.

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Evaluation

ARTICLE 13- (1) In bioequivalence studies, correction of pharmacokinetic parameters for differences in the assayed content of the test and reference batches is not expected. However, in exceptional cases where a reference product differing by less than 5% in the amount of active substance investigated cannot be found, correction for the amount of active substance may be acceptable. If a correction for the amount of active substance is to be made, this must be justified using the results obtained from the assay of the test and reference products and must be specified in the protocol. (2) Ideally, all volunteers enrolled in the study should be included in the statistical analysis. However, volunteers for whom evaluable data are obtained for neither the test nor the reference product in a cross-over design study (or for whom evaluable data are obtained for only one period in a parallel design study) should not be included in the analysis. (3) Data obtained from volunteers enrolled in the study should be treated equally. All volunteers participating in the study should be included in the analysis. (4) In studies with more than two treatment arms (for example, in a three-period study including two reference products, one from Türkiye and the other from the USA, or in a four-period study in which the test and reference products are investigated under both fed and fasted conditions), each comparison analysis should be performed without including data from treatment arms not relevant to the comparison being made. (5) In order for the evaluation of the results obtained from randomized studies to be unbiased, all volunteers must be observed and subjected to procedures according to the same rules. These rules must be independent of the procedures or the results. Therefore, the decision to exclude a volunteer from the statistical analysis must be made before bioanalysis. (6) In principle, for an exclusion reason to be considered valid, it must be specified in the protocol and the decision to exclude must be taken before bioanalysis. However, the non-inclusion of data should be avoided in order to meet the requirement of at least 12 volunteers for the evaluation to be performed and in order not to reduce the power of the study. (7) Events such as vomiting and diarrhoea that may render plasma concentration-time profile data unreliable are among the reasons requiring the non-inclusion of the results obtained from volunteers in a given period. In exceptional cases, concomitant medication use may also be a reason for excluding a volunteer. (8) If any of the conditions specified in the exclusion criteria set out in the protocol occurs, this must be recorded in the Case Report Form during the course of the study. The non-inclusion of a volunteer on the basis of these predefined criteria must be clearly described and listed in the study report. (9) Since formulation effects cannot be distinguished from other effects influencing pharmacokinetics, the non-inclusion of data on the basis of statistical analysis or solely for pharmacokinetic reasons is not acceptable.

(10) Exceptions to this situation: 1) In the case of a volunteer for whom no measurable concentration is obtained for the reference product or for whom only very low plasma concentrations are measurable, if the volunteer's AUC value is less than 5% of the geometric mean of the AUC values of the reference product (the geometric mean must be calculated without including data obtained from the volunteer with deviating values), that volunteer is considered to have very low plasma drug concentrations. The non-inclusion of data on this basis is acceptable only in exceptional cases and the validity of the study should be questioned. 2) Data from volunteers with non-zero baseline concentrations of more than 5% of Cmax should be excluded from bioequivalence calculations. (11) The reason for the occurrence of the exceptions mentioned above, in studies conducted with immediate release formulations, may be the volunteer's lack of compliance and an insufficient washout period. Such situations can be avoided by checking the volunteers' mouths after drug intake to ensure that they have swallowed the drug and by designing the study with a washout period of sufficient length. Samples taken from volunteers not included in the statistical analysis must nevertheless be subjected to assay and the results must be listed. (12) As stated in Article 10, the AUC(0-t) value should cover at least 80% of the AUC(0-∞) value. Even if the AUC(0-t) value covers less than 80% of the AUC(0-∞) value, the volunteers should be included in the statistical analysis. However, if this ratio is below 80% in more than 20% of the observations, the validity of the study should be discussed. This does not apply if the

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sampling period is 72 hours or longer and the AUC(0-72h) value is used instead of the AUC(0-t) value. (13) In studies designed to determine bioequivalence after a single dose, the parameters to be analysed are the AUC(0-t) (or AUC(0-72h), if applicable) and Cmax values. For these parameters, the 90% confidence interval for the ratio between the test and reference products must be within the acceptance range of 80.00%-125.00%. In order to be within the acceptance range, the lower limit must be ≥ 80.00%, rounded to two decimal places, and the upper limit must be ≤ 125.00%, rounded to two decimal places. (14) In studies designed to determine the steady-state bioequivalence of immediate release formulations, the AUC(0-τ) and Cmax,ss values must be analysed using the same acceptance range as described above. (15) In the rare cases where urinary data are used, Ae(0-t) and Rmax, respectively, must be analysed using the acceptance range described above for AUC(0-t) and Cmax. (16) No statistical evaluation of the tmax parameter is required. However, if rapid release is claimed to be clinically relevant and important for the onset of effect or associated with adverse events, there should be no marked difference between the test and reference products in the median value and variability of tmax.

(17) In special cases concerning products with a narrow therapeutic range, the acceptance range for AUC may need to be narrowed (see Article 15). In addition, for highly variable products, the acceptance range for Cmax may in certain cases be widened (see Article 16). (18) The bioequivalence assessment is based on the ratio of population geometric means (test/reference) within the 90% confidence interval of the parameters investigated. This method is equivalent to the two one-sided t-tests performed on the null hypothesis of non-bioequivalence at the 5% significance level. (19) The pharmacokinetic parameters to be evaluated must be analysed using ANOVA (analysis of variance). The data are subjected to logarithmic transformation before analysis. The confidence interval for the difference between formulations on the log-transformed scale is obtained from the ANOVA model. This confidence interval is then back-transformed to obtain the desired confidence interval for the ratio on the original scale. The performance of a non-parametric analysis is not acceptable. (20) The exact model to be used for the analysis must be specified in the protocol in advance. In the statistical analysis, the sources of variability assumed to have effects on the response variable must be taken into account. The terms to be used in the ANOVA model for cross-over designs are generally sequence, volunteer within sequence, period and formulation. (21) A test for carry-over effects should not be considered potentially meaningful. A decision regarding the analysis (for example, the analysis of the first period only) should not be made on the basis of such a test. The potential for carry-over effects should be addressed by designing the administration in the second period (and in subsequent periods, if applicable)

be assessed by examination of pre-dose plasma concentrations. If any participant has a pre-dose concentration greater than 5% of the Cmax value for that period, the statistical analysis is performed without including that participant's data for that period. In a two-period study, this will result in the participant being excluded from the analysis. If this results in fewer than 12 evaluable participants remaining, the study will not be considered acceptable. This approach is not appropriate for endogenous drugs. (22) In bioequivalence studies, the use of a two-stage approach may be acceptable if scientifically justified. An initial group of participants receives the drug and the data obtained are analysed. If bioequivalence is not demonstrated with this study, an additional group is enrolled and the data obtained from both groups are combined in the final analysis. If this approach is used, appropriate steps must be taken to preserve the overall type I error of the experiment, and the stopping criteria for the study must be clearly defined before the study commences. The analysis of the first stage data should be treated as an interim analysis, and both analyses should be performed using adjusted significance levels (hence, with confidence intervals based on a probability higher than 90%). For example, the use of 94.12% confidence intervals for both the first stage analysis and the combined data obtained from the first and second stages may be acceptable; however, numerous acceptable alternatives exist, and the choice of significance level (alpha) for the interim analysis is left to the study conductors. The plan for using

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a two-stage approach and the adjusted statistical significance levels to be used for each of the analyses must be specified in advance in the protocol. When analysing the combined data from the two stages, a stage term should also be included in the ANOVA model.

Presentation of Data

or not

ARTICLE 14- (1) All individual concentration data and pharmacokinetic parameters shall be presented together with their formulas as summary statistics such as geometric mean, median, arithmetic mean, standard deviation, coefficient of variation, minimum and maximum. Individual plasma concentration-time curves shall be presented on linear/linear and logarithmic/linear scales. The method used to derive the pharmacokinetic parameters from the raw data shall be specified. The number of points of the terminal log-linear phase used in the estimation of the terminal rate constant, which is required for a reliable AUC∞ estimate, shall be specified. (2) For the pharmacokinetic parameters subjected to statistical analysis, the 90% confidence interval and point estimates of the test/reference product ratio shall be presented. (3) ANOVA tables including appropriate statistical tests for all effects in the model shall be presented. (4) The report shall be prepared in sufficient detail to allow the pharmacokinetic and statistical analysis to be repeated. For example, the actual sampling times after dosing, drug concentrations, the values of the pharmacokinetic parameters for each volunteer in each period, and the randomization scheme shall be presented. (5) Volunteers who withdrew from the study and who were not included in the study shall be fully documented. Where possible, the concentration data and pharmacokinetic parameters of these volunteers shall be presented in a list for each volunteer, but shall not be included in the summary statistics. (6) The bioanalytical method shall be included in the pre-study validation report and shall be presented separately in the bioanalytical report. The bioanalytical report shall include a brief description of the bioanalytical method used and the results for all of the calibration standards and quality control samples. A representative number of chromatograms and other raw data covering the entire concentration range, for all standards and quality control samples and for the analyzed samples, shall be presented. This presentation shall include data containing chromatograms for at least 20% of the volunteers, together with the quality control samples and calibration standards. (7) If bioequivalence has been demonstrated in some but not all of the multiple studies conducted for a particular formulation at a particular strength, the results shall be evaluated as a whole. The existence of a study demonstrating bioequivalence does not mean that those failing to demonstrate bioequivalence can be disregarded. The applicant shall discuss the results obtained and justify the claim that bioequivalence has been demonstrated. Alternatively, where applicable, in addition to the individual study analyses, a pooled analysis of all the studies may also be presented. In cases where there is no study demonstrating bioequivalence, the evaluation of studies failing to demonstrate bioequivalence by pooling them is not acceptable.

Narrow therapeutic index drugs

ARTICLE 15- (1) For narrow therapeutic index drugs, the acceptance interval for AUC shall be narrowed to 90.00%-111.11%. Where Cmax is of particular importance for safety, efficacy, or therapeutic drug monitoring, the 90.00%-111.11% acceptance interval shall also be applied to this parameter. It is not possible to establish criteria for the definitive categorization of drugs as narrow therapeutic index drugs (NTIDs). Whether an active substance is an NTID shall be decided on a case-by-case basis, based on clinical assessments.

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Highly variable drugs

ARTICLE 16- (1) Highly variable drugs (HVDs) are products with within-subject variability greater than 30% for a given parameter. If the applicant suspects that the rate and/or extent of absorption of the drug is highly variable, a replicate, cross-over designed study may be conducted. (2) Where it is based on valid clinical justification that large differences in Cmax values are clinically irrelevant, a widened acceptance interval may be used in the evaluation of these HVDs. (3) For the widening of the acceptance interval, the bioequivalence study must have been conducted with a replicate (partial or full replicate) design, and it must have been demonstrated that the within-subject variability of the reference product used in the study exceeds 30% for the Cmax parameter. The applicant shall demonstrate that the calculated within-subject variability is a reliable estimate and is not a result arising from outliers. The request for widening of the interval shall be specified in the protocol. (4) If the ANOVA calculation was performed according to a fixed effect model, the widening applies only to Cmax, and its size can be defined based on the within-subject variability observed in the bioequivalence study using the scaled-average bioequivalence approach with the formula [U, L] = exp [±k × sWR] (In this formula, U and L are the upper and lower limits of the acceptance interval, respectively; k is the regulatory constant set at 0.760, and sWR is the within-subject standard deviation of the log-transformed values of Cmax for the reference product.). The table below provides examples of how different variability levels lead to different acceptance limits using this method. Within-subject CV (%) * Lower Limit Upper Limit 30 80.00 125.00 35 77.23 129.48 40 74.62 134.02 45 72.15 138.59 ≥ 50 69.84 143.19 CV(%)=100√(s2WR−1)

The geometric mean ratio must be within the conventional acceptance interval of 80.00%-125.00%. If the ANOVA calculation was performed according to a mixed effect model; the acceptance interval limits for Cmax can be widened by calculating with the formula e^(±Swr×0.893), where s2WR = ln((CV2WR)+1). (5) The widening of the acceptance criteria based on high within-subject variability does not apply to AUC; the acceptance interval for AUC must be 80.00%-125.00% regardless of variability. (6) In a replicate design study, the use of a three- or four-period cross-over design (partial or full replicate) is acceptable.

In vitro dissolution tests complementary to bioequivalence studies

ARTICLE 17- (1) The results of in vitro dissolution tests, conducted in three different buffers (normally at pH 1.2, pH 4.5, and pH 6.8) and in the medium required for the release of the finished product (quality control medium) for the test and reference product batches used in the bioequivalence study, shall be presented. For orally disintegrating tablets and similar special dosage forms, the study may need to be conducted under different experimental conditions. The results shall be presented as percent drug dissolved-time profiles, including mean values and summary statistics. Unless otherwise specified, the in vitro dissolution specifications used in the quality control of the product shall be determined according to the dissolution profile of the test product batch that is bioequivalent to the reference product (see Annex-2). (2) If the results obtained from the comparative in vitro dissolution test for the batches do not reflect the bioequivalence demonstrated in vivo, the in vivo data shall be taken into account. However, the possible reasons for this discrepancy shall be addressed and this situation shall be justified.

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In vitro dissolution tests supporting biowaiver of strengths

ARTICLE 18- (1) Appropriate in vitro dissolution data should confirm that a waiver may be applied in addition to in vivo bioequivalence testing. Where a waiver of the other strengths from in vivo studies is at issue, in addition to an in vivo study with the appropriate strength, comparative in vitro dissolution studies must be conducted at different pH values (normally pH 1.2, pH 4.5 and pH 6.8) between two pilot or full-scale production batches of the other strengths and the bioseries of the test product. In addition, comparative in vitro dissolution studies performed with the bioseries of the reference product should be submitted as supporting data. (2) At pH values where sink conditions cannot be achieved for all strengths, in vitro dissolution may differ between different strengths. It should be demonstrated, by comparison with the relevant strength of the reference product, that this finding is related to the active substance rather than to the formulation. In addition, the applicant should demonstrate the similarity of dissolution profiles at the same dose (one 10 mg tablet may be compared with two 5 mg tablets).

Bioequivalence study report

ARTICLE 19- (1) The bioequivalence study report should provide complete documentation on the study protocol, its conduct and evaluation. The submitted report should include: • Summary Report (see Annex-5) • Study Review Form (see Annex-6) • Final Report (including the study protocol), • Bioanalytical Study Report • Statistical data • In vitro dissolution studies (including assay method, analytical method validation, comparative dissolution test results of the test and reference products, and similarity test results), • Literature • Other documents (protocol approval letter, ethics committee approval letter, sample informed consent form of the volunteers, reference product procurement document, GCP Document (where available, certificates of the monitors), other accreditation documents, active substance, certificate of analysis of the test and reference products, and unit formula of the test product). This report should be prepared in accordance with the ICH E3 guideline, the required sections should be signed, and it should be presented in full in Module 5. (2) For submission upon request, data sufficiently detailed to allow the repetition of the pharmacokinetic and statistical analysis (for example, actual sampling times, drug concentrations, pharmacokinetic parameter values for each subject in each period, and the randomization scheme) should be retained in a suitable electronic format (for example, in Excel format).

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Variation applications

ARTICLE 20- (1) Where a change has been made to the initially approved formulation of the product or to the manufacturing method of the product that may affect bioavailability, an in vivo bioequivalence study must be conducted, unless otherwise specified. All justifications submitted should be based on general considerations, on the basic requirements as set out in Annex-4, or on whether an acceptable Level A in vitro/in vivo correlation has been established. (2) Where the bioavailability of the changed product has previously been examined and an acceptable Level A correlation has been established between in vivo performance and in vitro dissolution, and where the dissolution profile of the new product is similar to that of the approved product under the same test conditions under which the correlation was established, in vivo bioequivalence may not need to be demonstrated (see Annex-2). (3) In the case of variations made to licensed reference medicinal products, the product currently registered with information on its formulation, manufacturing process, packaging and similar details should generally be used as the comparator product in bioequivalence and dissolution studies. (4) Where a variation is to be made to a generic medicinal product or a hybrid product, a current batch of the reference product should generally be used in the bioequivalence study. Where no valid reference product is available on the market, a comparison with the previous formulation of the reference medicinal product may be acceptable, provided that it is justified. For changes that do not require a bioequivalence study, the recommendations and requirements specified in the other relevant published guidelines should be followed.

Other matters

ARTICLE 21- (1) General information on the bioequivalence study requirements for different dosage forms is provided in Annex 3. (2) This guideline should be evaluated together with the relevant guidelines on pharmaceutical quality.

Repealed Legislation

ARTICLE 22- (1) The Guideline on the Selection of the Reference Product to be Used in Bioavailability and Bioequivalence Studies of Human Medicinal Products, dated 28.07.2017, has been repealed. Entry into force:

ARTICLE 22- (1) This Guideline enters into force upon the approval of the President of the Agency. (2) The third paragraph of Article 5 of this Guideline enters into force on 01.01.2023. Execution:

Annex-1 Abbreviations Ae(0-t): The cumulative amount of unchanged drug excreted in urine up to time point t after drug administration, Residual area: The extrapolated area (AUC(0-∞) – AUC(0-t)) / AUC(0-∞), Cmax: Maximum plasma concentration, Cmax,ss: Maximum plasma concentration at steady state, AUC(0-t): The area under the plasma concentration curve for the portion up to the last observed concentration at time t after drug administration, AUC(0-∞): The area under the plasma concentration curve extrapolated to infinite time, AUC(0-τ): The AUC over one dosing interval at steady state, AUC(0-72h): The area under the plasma concentration curve up to the 72nd hour after drug administration, SPC: Summary of product characteristics, Rmax: The maximum rate of urinary excretion of the drug, tmax: The time elapsed until the Cmax value is reached, tmax,ss: The time elapsed until the Cmax,ss value is reached, t1/2: The plasma concentration half-life, λz: The terminal rate constant,

shall denote.

Annex-2 Dissolution testing and similarity of dissolution profiles 1. General aspects regarding dissolution tests related to bioavailability Dissolution studies: 1) To test product quality; • To obtain supporting information for quality control specifications regarding the test product series used in bioavailability/bioequivalence studies and clinical studies, • To use as a quality control tool to demonstrate continuity/consistency in manufacturing, • To obtain information regarding the reference product used in bioavailability/bioequivalence studies and clinical studies, 2) To make

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inferences substituting for bioequivalence; • To demonstrate similarity between different formulations of an active substance and the reference product in certain cases (e.g., to obtain a biowaiver for variations, during development or during formulation changes in equivalent medicinal products; see Annex-4) • To examine batch-to-batch consistency of products (test and reference) in selecting suitable batches to be used in an in vivo study, are performed. Test methods shall be developed for the relevant product on the basis of general and/or pharmacopoeial requirements. Where these conditions remain insufficient and/or they do not reflect in vivo dissolution (biorelevance), alternative methods may be considered, provided that they are demonstrated to be discriminating and capable of distinguishing between acceptable and unacceptable batches in terms of the in vivo performance of the product. Current information, including the interaction between the Biopharmaceutics Classification System (BCS) and the properties obtained from the dosage form, shall always be taken into consideration. Sampling time points shall be at intervals of no less than 15 minutes and sufficient to obtain meaningful dissolution profiles. More frequent sampling is recommended in the time period where the greatest change in the dissolution profile occurs. For products exhibiting complete dissolution (rapidly dissolving) within 30 minutes, sampling at 5- or 10-minute intervals may be required to reveal an appropriate and adequate profile. If an active substance is highly soluble, the dosage system dissolves rapidly within the physiological pH range, and the excipients are known not to affect bioavailability, the active substance is considered to have no bioavailability problem. In contrast, if an active substance has limited or low solubility, the rate-limiting step in its absorption may be the dissolution of the dosage form. This also applies in cases where the release and, subsequently, the solubility of the active substance are controlled by excipients; in such cases, it is recommended to apply various test conditions while ensuring adequate sampling.

2. Similarity of dissolution profiles

Dissolution profile similarity testing and any inference drawn from the results (e.g., a justification for a biowaiver) can only be considered valid if the dissolution profile has been adequately characterized using a sufficient number of time points. For immediate-release formulations, the comparison made at 15 minutes is important for determining that complete dissolution is achieved before gastric emptying. Where more than 85% of the drug dissolves within 15 minutes, the dissolution profiles may be accepted as similar without the need for further mathematical evaluation. Where more than 85% of the drug does not dissolve within 15 minutes but dissolves within 30 minutes, at least three time points are required: the first before the 15th minute, the second at the 15th minute, and the third at a point close to 85% dissolution. The similarity of dissolution may be determined using the f2 statistic, as shown below: &#3627408467; 2=50.log [

100 √ 1+ ∑ [?????? (??????) –?????? (??????)] 2 ??????=?????? ??????=1 ??????]

In this equation, f2: similarity factor, n: the number of time points, R(t): the mean percentage of the reference product dissolved at time point t after the start of the study, T(t): the mean percentage of the test product dissolved at time point t after the start of the study. The percentage dissolved shall be determined for both the reference and the test formulations. The evaluation of the similarity factor is based on the following conditions: • There shall be at least three time points (excluding zero), • The time points shall be the same for both formulations, • There shall be 12 values for each time point for each formulation, • There shall be no more than one mean dissolution value above 85% for all the formulations, • For any product, the relative standard deviation or coefficient of variation shall be less than 20% for the first point and less than 10% for the other time points. An f2 value between 50 and 100 indicates that the two dissolution profiles are similar. Where the f2 statistic is not appropriate, the similarity assessment may be performed using model-dependent or model-independent methods (e.g., comparison of Weibull function parameters or of dissolution percentages at different time points using multivariate statistics).

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These methods are acceptable provided that they are statistically valid and adequately justified. The similarity acceptance limits shall be predetermined, justified, and shall not be greater than a 10% difference. Furthermore, the dissolution variability of the test and reference product data shall also be similar; however, a lower variability for the test product may also be acceptable. Evidence demonstrating that the statistical software has been validated shall also be submitted. Clear definitions and descriptions of the steps in the application of the method shall be presented together with appropriate summary tables.

Annex-3 Bioequivalence study requirements for different dosage forms Although this guideline relates to immediate-release formulations, this section provides some general information on bioequivalence studies with other formulation types and specific types of immediate-release formulations. If the test product contains a different salt, ester, ether, isomer, mixture of isomers, complex or derivative of the reference product active substance, bioequivalence shall be demonstrated by in vivo bioequivalence studies.

However, when the active substance in both the test and reference products is identical (or, as also stated in Annex-4, Section III, when they contain salts exhibiting similar properties), in vivo bioequivalence studies may not be required in certain cases, as described below and in Annex-4.

Immediate-release oral dosage forms acting systemically

For dosage forms such as tablets, capsules and oral suspensions, bioequivalence studies must be conducted unless a biowaiver is applicable (see Annex-4). For orodispersible tablets and oral solutions, the following recommendations apply.

Orodispersible Tablets

Orodispersible tablets (ODTs) are formulated on the basis of rapid disintegration in the mouth. In cases where the active substance also dissolves in the mouth and is absorbed directly via the buccal mucosa, the placement of the tablet in the mouth and the contact time may be parameters of critical importance. Depending on the formulation, the coated substance may, for example, be swallowed and subsequently absorbed from the gastrointestinal tract. A BCS-based biowaiver may be applicable if it can be demonstrated that the active substance is not absorbed in the oral cavity but is instead swallowed and absorbed via the gastrointestinal tract (see Annex-4). If this cannot be demonstrated, bioequivalence must be assessed by means of studies in humans.

If the ODT test product is a variation of another oral formulation, a 3-period study is recommended in order to evaluate both the administration of the orodispersible tablet with concomitant liquid intake and without liquid intake. However, if bioequivalence is demonstrated in a 2-period study between the ODT taken without water and the reference formulation taken with water, the ODT taken with water may also be assumed to be bioequivalent.

If the ODT is a generic medicinal product/hybrid product of an approved ODT reference product, the following recommendations regarding study design apply:

• If the reference product can be taken with or without water, bioequivalence should be demonstrated for use without water, since this is the condition most resembling the mode of use of the formulation. This is particularly important if the substance has the potential to dissolve and be partially absorbed in the oral cavity. If bioequivalence is demonstrated for use without water, the product may also be assumed to be bioequivalent when taken with water.

• If the reference product is taken by a single route only (e.g. only with water), bioequivalence must be demonstrated under this condition (using a conventional two-way crossover design).

• If the reference product is taken by only a single route (e.g. only with water) and additional routes of administration are intended to be developed for the test product (e.g. without water), both the conventional and the new method should be compared with the reference product administered by the conventional route (3 administrations, 3 periods, 6-sequence design).

In studies where ODTs are evaluated with administration without water, it is recommended that the mouth be moistened by swallowing 20 mL of water immediately before placing the tablet on the tongue, and that liquid intake be permitted no earlier than 1 hour after administration.

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Other oral formulations such as orodispersible films, buccal tablets or buccal films, sublingual tablets and chewable tablets may be addressed in a manner similar to ODT administration. Bioequivalence studies should be performed in accordance with the proposed mode of use of the product.

Oral Solutions

If the test product is an aqueous oral solution at the time of administration and contains the active substance at the same concentration as an approved oral solution, bioequivalence studies may be waived. However, if the excipients it contains may affect the gastrointestinal transit of the active substance (e.g. sorbitol, mannitol, etc.), its absorption (e.g. surfactants or excipients that may affect carrier proteins), its in vivo solubility (e.g. co-solvents) or its in vivo stability, and if the differences in the amounts of these excipients cannot be adequately justified with reference to other data, a bioequivalence study must be conducted. The requirements foreseen regarding the similarity of excipients with respect to biowaiver (see Annex-4, Section IV.2 Excipients) also apply to oral solutions.

In cases where the test product is intended to be bioequivalent to another immediate-release oral dosage form, bioequivalence studies must be conducted.

Modified-release pharmaceutical dosage forms

In studies to be conducted for modified-release pharmaceutical dosage forms, the general principles set out in the guideline published by the EMA entitled "Guideline on the pharmacokinetic and clinical evaluation of modified release dosage forms — EMA/CPMP/EWP/280/96" should be taken into consideration.

Fixed-combination dosage forms

In studies to be conducted for fixed-combination products, the general principles set out in the guideline published by the EMA entitled "Guideline on clinical development of fixed combination medicinal products — EMA/CHMP/158268/2017" should be taken into consideration. Information on the possibility of a biowaiver for fixed-combination products is provided in Annex-4, Section V.

Immediate-release systemically acting dosage forms not administered by the oral route

This section concerns dosage forms such as rectal formulations. In general, bioequivalence studies must be conducted. A biowaiver may be considered for a solution containing the active substance at the same concentration as an approved solution and having the same qualitative and similar quantitative composition in terms of excipients (the conditions under the heading oral solutions may be applied).

Parenteral solutions

If the test product is to be administered as an aqueous solution containing the same active substance as the currently approved product, bioequivalence studies are generally not required. However, if any of the excipients interacts with the active substance (e.g. complex formation) or affects the disposition of the active substance, and both products do not contain the same excipients in very similar amounts, and the absence of an effect of this difference on the pharmacokinetics of the active substance cannot be adequately justified, a bioequivalence study must be conducted.

In the case of other parenteral routes of administration such as intramuscular or subcutaneous; where the test product is of the same solution type (aqueous or oily) as the currently approved product and contains the same active substance at the same concentration and the same excipients in similar amounts, bioequivalence studies are not required. Furthermore, if it can be demonstrated that the excipients have no effect on viscosity, bioequivalence studies are not required for parenteral aqueous solutions containing comparable excipients in similar amounts.

Liposomal, micellar and emulsion dosage forms for intravenous use

• Liposomal formulations: Pharmacokinetic considerations relating to intravenously administered liposomal formulations are outside the scope of this guideline.

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• Emulsions: A biowaiver is not applicable to emulsions. However, a biowaiver assessment may be performed in the following two cases: a) If the finished product is not designed to control release or drug disposition, b) If the method and rate of administration are the same as those of the currently approved product.

In such cases, the composition of the product must be qualitatively and quantitatively identical to that of the currently approved emulsion, sufficient data must be submitted to demonstrate that it has similar physicochemical properties, including the size distribution of the dispersed lipid phase, and these data must be supported by other relevant valid emulsion characteristics (e.g. surface properties such as Zeta potential and rheological properties).

• Lipids for intravenous parenteral nutrition: For intravenous parenteral nutrition

k sufficient data are submitted demonstrating that comparable physicochemical properties exist for lipids, a biowaiver evaluation may be conducted. Differences in composition may be justified taking into account the nature and therapeutic objectives of such dosage forms.

• Micelle-forming formulations: Micellar solutions for intravenous administration may be considered as 'complex' solutions and are therefore normally not suitable for a biowaiver. However, a biowaiver evaluation may be conducted if the following situations apply: a) If the micelles rapidly dissociate upon dilution and are not intended to control the design, release or distribution of the finished product, b) If the method and rate of administration are the same as those of the currently approved product, c) If the excipients do not affect the disposition of the active substance. In such cases, the composition of the micellar infusion immediately prior to administration must be qualitatively and quantitatively identical to the composition of the currently approved product, and sufficient data must be submitted to demonstrate similar physicochemical properties. For example: critical micelle concentration, solubilisation capacity of the formulation (such as maximum additive concentration), free and bound active substance, and micelle size. A biowaiver evaluation may also be conducted in cases of minor quantitative or qualitative changes in the composition of the formulation, except for changes in the amount or type of surfactants. Locally applied, locally acting products For locally applied, locally acting products, the guidelines published by the EMA entitled "Clinical Requirements for Locally Applied, Locally Acting Products containing Known Constituents (CPMP/EWP/239/95)" and "Guideline on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) Including the Requirements for Demonstration of Therapeutic Equivalence Between Two Inhaled Products for Use in the Treatment of Asthma and Chronic Obstructive Pulmonary Disease (COPD) in Adults and for Use in the Treatment of Asthma in Children and Adolescents (CPMP/EWP/4151/00 rev 1)" should be taken into consideration. For solutions (for example eye drops, nasal sprays or solutions applied to the skin), if the test product is of the same type as the currently approved solution product (aqueous or oily) and contains the same active substance at the same concentration, it may not be necessary to submit equivalence data. Minor differences in excipients may be acceptable if the relevant pharmaceutical characteristics of the test and reference products are identical or essentially similar. Qualitative and quantitative differences in excipients must be justified in terms of therapeutic equivalence. Unless otherwise stated, the route and method of administration must be the same as those of the currently approved product. Where systemic exposure arising from locally applied, locally acting products entails a risk of systemic adverse reactions, systemic exposure must be measured. It must be demonstrated that systemic exposure for the test product is not higher than that of the reference product, and the upper limit of the 90% confidence interval must not exceed 125.00, the upper limit of the bioequivalence acceptance interval.

Gases If the product is a gas for inhalation, bioequivalence studies need not be performed.

Annex-4 Biowaiver based on the Biopharmaceutics Classification System (BCS) I. Introduction In the BCS-based biowaiver approach, in vivo bioequivalence studies may be waived if the assumption of equivalence in in vivo performance can be justified with in vitro data. The BCS-based biowaiver application is limited to active substances with known human absorption, not

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considered to have a narrow therapeutic index, and exhibiting high solubility. This approach is applicable to immediate-release solid pharmaceutical products for oral use and systemic action in the same pharmaceutical form. However, it is not applicable to sublingual, buccal and modified-release formulations. For orodispersible formulations, the BCS-based biowaiver approach may be applied in cases where there is no absorption in the oral cavity. This approach may be used for equivalent medicinal products, variations of innovative products, variation applications requiring bioequivalence studies, and to demonstrate bioequivalence between early clinical trial products and the products to be marketed. II. Summary of Information For immediate-release products, the BCS-based biowaiver approach may be applied when the following conditions are met: • If the active substance has been demonstrated to exhibit high solubility and complete absorption (BCS-class I) (see section III), and - Demonstration, taking into account the specific requirements, that the test and reference products have either very rapid (>85% within 15 minutes) or similarly rapid (85% within 30 minutes) in vitro dissolution characteristics (see section IV.1), and - That excipients affecting bioavailability are qualitatively and quantitatively the same (in general, the use of the same excipients in similar amounts is preferred) (see section IV.2). • If the active substance has been demonstrated to exhibit high solubility and limited absorption (BCS-class III) (see section III), and - Demonstration, taking into account the specific requirements, that the test and reference products have very rapid (>85% within 15 minutes) in vitro dissolution characteristics (see section IV.1), and - That excipients affecting bioavailability are qualitatively and quantitatively the same, and that the other excipients are qualitatively the same and quantitatively very similar (see section IV.2). Due to the risk of reaching an inappropriate biowaiver decision, products containing BCS-class III active substances must be evaluated more cautiously than products containing BCS-class I active substances (for example,

region-specific absorption, risk of transporter protein interactions at the site of absorption, excipient composition and therapeutic risks). III. Active substance To characterise the active substance properties relevant to biowaiver for known compounds, literature published in recognised, peer-reviewed journals is generally accepted. If the active substances in the test and reference products are identical, a biowaiver may be applied. In addition, a biowaiver may be applied in cases where the products contain different salts, provided that both are BCS-class I (high solubility and complete absorption; see sections III.1 and III.2). A biowaiver is not applicable where the test product contains a different ester, ether, isomer, mixture of isomers, complex or derivative of the active substance in the reference product, because this difference may result in bioavailability differences that cannot be understood by inference from the tests used in the BCS-based biowaiver approach. The active substance must not belong to the group of drugs with a narrow therapeutic index. III.1 Solubility The pH-solubility profile of the active substance must be determined and discussed. The active substance is considered highly soluble if the highest single dose administered in immediate-release dosage form is fully dissolved at 37±1°C in 250 mL buffers over the pH range 1-6.8. To demonstrate solubility, investigations must be conducted in at least three different buffers within this range (preferably at pH 1.2, pH 4.5 and pH 6.8, and additionally at the pKa if it is within the specified pH range). To reach a definitive solubility classification, repeated determinations under each of the pH conditions may be necessary (for example, the shake-flask method or other validated methods). The pH of the solution must be verified before and after the addition of the active substance to the buffer solution.

III.2 Absorption In biowaiver applications based on the BCS, demonstration of complete absorption in humans is preferred. In this context, complete absorption is considered to be the case where the extent of absorption measured is 85% or greater, and it is generally associated with high permeability. For the determination of complete drug absorption, data obtained from • Absolute bioavailability or • Mass balance studies may be used. When data from mass balance studies are used, it must be ensured that the metabolites taken into account in the determination of the absorbed fraction are formed after absorption. Therefore, when reference is made to the total radioactivity excreted in urine, it must be ensured that the unchanged active substance

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present in gastric or intestinal fluid has not degraded or been metabolized. Phase 1 oxidative and Phase 2 conjugative metabolism can only occur after absorption (they do not occur in gastric or intestinal fluid). Therefore, if the urinary recovery of the parent compound together with the sum of the urinary and faecal recoveries of Phase 1 oxidative and Phase 2 conjugative drug metabolites corresponds to 85% or more of the dose, the data from mass balance studies support complete absorption. In addition, highly soluble active substances that are not completely absorbed, such as BCS class III compounds, may be considered for a biowaiver provided that the prerequisites related to the composition of the product and in vitro dissolution are fulfilled (see section IV.2). More restrictive requirements will also be applied to compounds that are predicted to be BCS class I but for which complete absorption has not been demonstrated with a convincing level of evidence. The reported bioequivalence found between aqueous and solid formulations of a particular compound administered by the oral route may be supportive, as it may suggest that absorption limitations arising from the characteristics of immediate-release formulations are negligible. Well-designed and properly conducted in vitro permeability studies, including reference standards, may also be used as supporting in vivo data. IV. Finished product IV.1 In vitro dissolution IV.1.1 General aspects Assessments of products should confirm immediate-release properties and demonstrate that the test and reference products exhibit similar in vitro dissolution profiles under physiologically relevant experimental pH conditions. However, this does not demonstrate the existence of an in vitro/in vivo correlation. In vitro dissolution should be investigated over the pH range of 1 – 6.8 (at least at pH 1.2, pH 4.5 and pH 6.8). Additional investigations may need to be performed at pH values where the active substance exhibits its lowest solubility. The use of surfactants is not acceptable. The test and reference products should meet the conditions specified in Article 7. In accordance with these conditions, the investigation of more than one batch of the test and reference products is recommended. In comparative in vitro dissolution experiments, current pharmacopoeial standards should be followed. Therefore, complete descriptions of the experimental conditions and analytical methods, including validation data, should be provided. In order to perform a statistical evaluation, the use of 12 units of product per experiment is recommended. General experimental conditions are exemplified below: • Apparatus: Paddle or basket • Volume of dissolution medium: 900 mL or less • Temperature of the dissolution medium: 37°C ± 1°C, Agitation: Paddle – generally 50 rpm Basket – generally 100 rpm • Sampling time points: 10, 15, 20, 30 and 45 minutes • Buffers: pH 1.0 – 1.2 (generally, simulated gastric fluid without enzymes or 0.1 N HCl), pH 4.5 and pH 6.8 (or simulated intestinal fluid without enzymes); (pH levels should be maintained throughout the experiment) • Other conditions: Surfactants should not be used; in the case of gelatin capsules or tablets with gelatin coatings, the use of enzymes may be acceptable. Complete documentation of the in vitro dissolution experiments (including the study protocol, information on the test and reference batches, detailed experimental conditions, method validation, individual and mean results and the relevant summary statistics) should be provided. IV.1.2. Evaluation of in vitro dissolution results Finished products in which more than 85% of the labelled amount dissolves within 15 minutes are considered "very rapidly" dissolving. If this is achieved for both the test and reference products, the dissolution profiles are considered similar without any mathematical treatment. Where more than 85% of the labelled amount dissolves in more than 15 minutes but less than 30 minutes, it may be concluded that no significant differences exist with respect to dissolution, i.e. similarity is demonstrated. The f2 test or other appropriate tests should be applied to establish the similarity of the dissolution profiles of the test and reference products. Since dissolution profile assessments do not reflect an in vitro/in vivo correlation, it is not appropriate to discuss the differences found here in terms of clinical/therapeutic significance. IV.2 Excipients In general, although excipients in immediate-release dosage forms are considered to have no effect on the bioavailability of active substances belonging to BCS class I, this cannot be entirely disregarded. Therefore, for medicinal products containing active substances belonging to BCS class I as well, it is recommended that the same excipients used in the reference product be used in similar quantities in the test product. If a

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biowaiver is to be applied for active substances belonging to BCS class III, the excipients should be qualitatively the same and quantitatively very similar, in order to rule out any different effects of the excipients on membrane transporters. As a general rule, in products containing active substances belonging to both BCS class I and class III, well-known excipients should be used in known amounts, and interactions that may affect drug bioavailability and/or solubility characteristics should be taken into consideration. Together with a justification that the quantity of each excipient is within the normal range, a description of the functions of the excipients should be provided. Excipients that may affect bioavailability, such as sorbitol, mannitol, sodium lauryl sulfate and other surfactants, should be identified and assessed together with their propensity to interact with the active substance (e.g. complex formation), their effects on gastrointestinal motility, drug permeability and their potential to interact with membrane transporters. Excipients that may affect bioavailability should be qualitatively and quantitatively the same in the test and reference products. V. Fixed dose combinations (FDC) The BCS-based biowaiver approach may also be applicable to immediate-release FDCs, provided that all of the active substances contained in the fixed dose combinations belong to BCS class I or III and the excipients fulfil the conditions outlined in section IV.2. In cases where these conditions are not met, in vivo bioequivalence testing must be performed.

Annex-5 Summary Report 1) Name of the product 2) Unit formulae and doses (if there are different doses, comparative unit formulae should also be provided in tabular form) 3) Summary of the in vivo study • Title of the study • Name and address of the CRO (Contract Research Organization) • Name and address of the clinical centre • Name and address of the analytical centre • Test product; Name Marketing authorisation holder and manufacturing site Batch number Dates of manufacture and expiry • Reference product; Name Marketing authorisation holder and manufacturing site Batch number

strength Manufacturing and expiry dates • Reference product procurement document • Washout period • Number of volunteers (number at study start and number included in the statistical calculation) • Brief information on the analytical method (equipment used, substance or substances quantified, extraction method, LOQ (limit of quantification), working range) • Results (test/reference AUC with Cmax and CV values) and interpretation 4) Physicochemical and pharmacokinetic properties of the active substance • Solubility • Bioavailability • Cmax, tmax, elimination half-life • Volume of distribution • Protein binding • Food effect • AUC • Metabolism and metabolites • Excretion Note: The pharmacokinetic parameters section must be presented in tabular form. 5) In vitro studies • In vitro dissolution method, summary results table and profiles of mean values 6) Protocol approval letter *In bioavailability studies, information on the comparator product must be submitted.

Annex-6 Study Review Form The form must be adapted to the study design for the submission of bioavailability studies. BIOEQUIVALENCE STUDY REVIEW FORM DATE:

PDF/ Page No: Review Notes Product name, Applicant:
Active substance
Indication
Imported/Manufactured
Evaluation of fk, fd data (theoretical) tmax:
t1/2:
Metabolite:
Half-life (obtained from study results) Test: Reference:
Analytes evaluated
Matrix used
Fasted/fed study
Clinical center
Analytical center
CRO (Contract Research Organization)

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PDF/ Page No: Review Notes Test product name Marketing authorization holder Manufacturing site Batch number Expiry date Test biobatch batch size (indicate if it is a Know-How file)

Source of active substance

Reference product name Marketing authorization holder Manufacturing site Batch number Expiry date

Reference product procurement document containing batch number and expiry date information:

GCP-related documents

Blood sampling period

Washout period

Clinical study start date

Analytical study start date

Analytical method validation date

Analytical reporting date

Final reporting date

Statistical data

PDF/ Page No: Review Notes

Number of volunteers

Dosed Completed the study Included in the statistical calculation

Reasons for withdrawal of volunteers

Pharmacokinetic profiles of all volunteers (yes/no)

Pharmacokinetic values of all volunteers (yes/no)

Study design used

Statistical calculation method used

90% confidence interval Cmax AUC0-t AUC0-∞

Intra-subject variability (intra subject cv) Cmax AUC0-t AUC0-∞

Statistical power

ANOVA tables provided for all parameters? (yes/no)

Analytical Method PDF/ Page No: Review Notes Equipment used Extraction method Information on how the test was performed (yes/no)

Information on other equipment and solvents used (yes/no)

Analytical Validation date Dates of volunteer sample analysis Limit of quantification (LOQ) Working range (Range) Selectivity (selectivity, specificity) (with matrix obtained from at least 6 different sources)

Accuracy

Precision

Linearity

Recovery

Stability long-term short-term freeze-thaw autosampler stock solution

Raw data (at least 20%) (yes/no)

In-study control samples

QC1 QC2 QC3 QC4 mean accuracy % cv/sd Limit of detection (LOD), robustness, consistency

In Vitro Dissolution Test Studies for the Strength Subjected to In Vivo BE Study

PDF/ Page No: Review Notes Equipment and method used in the dissolution test Analysis method, information on the medium in which the study was conducted

Information on other equipment and solvents used

Test product batch no/Reference product batch no Dissolution profiles of the comparative dissolution test studies conducted with the reference medicinal product

Individual presentation of data

Study results:

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mean % RSD for test and reference

f2 values Validation date Sample chromatograms/spectra Selectivity (selectivity, specificity) Accuracy Precision repeatability intermediate precision reproducibility

Linearity LOQ/Calibration range Stability

In Vitro Dissolution Test Studies for Other Strengths

Product name, Applicant PDF/ Page No: Review Notes Active substance Dose proportionality

Linear Pharmacokinetics

Strength for which an in vivo BE study was conducted

Equipment and method used in the dissolution test Analysis method, information on the medium in which the study was conducted

Information on other equipment and solvents used

Test product batch no/Reference product batch no Dissolution profiles of the comparative dissolution rate studies conducted with biobatches

Individual presentation of data

Study results: mean % RSD for test and reference

Validation date Sample chromatograms/spectra f2 values Selectivity (selectivity, specificity) Accuracy Precision repeatability intermediate precision reproducibility

Linearity LOQ / Calibration range Stability

In Vitro Dissolution Test Studies for Products Exempt from In Vivo Studies

Product Name, Applicant PDF/ Page No: Review Notes Active Substance Justification for Exemption Equipment and method used in the dissolution test Analysis method, information on the medium in which the study was conducted

Information on other equipment and solvents used

Test product batch no/Reference product batch no Dissolution profiles of the comparative dissolution rate studies conducted with the reference product

Individual presentation of data

Study results:

mean % RSD for test and reference

Validation date Sample chromatograms/spectra F2 Values Selectivity (Selectivity, specificity) Accuracy Precision Repeatability Intermediate precision Reproducibility

Linearity LOQ / Calibration range

Stability

lite

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