ANNEX
to the Decision of the Council of the
Eurasian Economic Commission
No. dated 20

ANNEX No. 10
to the Rules for Conducting
Bioequivalence Studies of Medicinal
Products within the Eurasian
Economic Union

GUIDELINES
on the Pharmacokinetic and Clinical Study of Bioequivalence of Modified Release Medicinal Products

I. Introduction

1. The Annex to the Rules for Conducting Bioequivalence Studies of Generic Medicinal Products within the Eurasian Economic Union (hereinafter – the Annex) on Pharmacokinetic and Clinical Study of Bioequivalence of Modified Release Medicinal Products (hereinafter – the Annex) is designed to harmonize the legislation of international treaties and acts constituting the law of the Eurasian Economic Union (hereinafter – the EAEU, the Union) in the field of circulation of medicinal products with the European Union's legislation in this field.

2. The purpose of these Guidelines is to define the studies required to determine the efficiency, safety, biopharmaceutical and pharmacokinetic properties of modified release medicinal products after oral administration, intramuscular and subcutaneous injections, and transdermal dosage forms in humans, and to establish General principles for designing, conducting and evaluating the results of respective studies.

3. Each of the circumstances in which a modified release product may be developed requires separate recommendations and standards. These circumstances may be divided into three groups:

marketing authorization of modified release medicinal products of new chemical entities;

marketing authorization of a modified release medicinal product, the active substance of which is authorized to be marketed within the composition of the product of a different release rate (for example, an immediate release product);

abridged marketing authorization of a modified release medicinal product referring to a commercial medicinal product with modified release, for example, marketing authorization as a generic or hybrid medicinal product.

4. This Annex also includes recommendations for bioequivalence studies of generic prolonged release and delayed release medicinal products.

5. In each specific case, the types and number of studies to be performed should be determined based on the properties, scope, dosage form and intended therapeutic use of the medicinal product.

II. Definitions

6. For the purposes of these Guidelines, the following terms shall be used, their meanings set forth in the respective definitions below:

«intramuscular (subcutaneous) depot formulation» – shall mean a medicinal product for intramuscular or subcutaneous administration, which releases its active substance continuously over a certain period of time. Subcutaneous depot formulations include implants;

«biphase release formulation» – shall mean a dosage form in which the first phase is determined by the fast release dose fraction providing a therapeutic concentration of the active substance for a short period of time after administration. During the second extended phase, the dose fraction required to maintain an effective therapeutic concentration of the active substance over a prolonged period of time is released;

«immediate release dosage form, immediate release formulation» – shall mean a dosage form/formulation, in which the rate and (or) time, and (or) place of release of the active pharmaceutical substance is not modified by the introduction of special excipients and (or) the use of special manufacturing technology;

«delayed release dosage form, delayed release formulation» – shall mean a dosage form/formulation, in which the release of the active substance is delayed for a certain period of time after administration of the dosage. The subsequent release is similar to that of an immediate release dosage form;

«pulsatile release dosage form» – shall mean a dosage form with immediate release of the active substance at specific time intervals;

«multiple-unit dosage form» – shall mean a dosage form containing a plurality of units (for example, pellets or granules), each containing release controlling excipients, for example, in a gelatin capsule or compressed in a tablet;

«single-unit dosage form» – shall mean a dosage form consisting of only one unit, for example, osmotic tablet;

«transdermal patch, transdermal drug delivery system» – shall mean a semi-solid of medicinal product of varying size containing one or more active substance(s) to be applied on the intact skin for systemic availability.

There are two main types of transdermal patch depending on the method how the active substance in patch components is dispersed:

matrix, with the active substance release by diffusion;

reservoir, with a membrane-controlled release of the active substance from the liquid compartment.

III. Basis for Development

7. The development of a medicinal product with modified release of the active substance should be based on a well-defined clinical need (for example, increased responsiveness and (or) patient safety) and on an integration of physiological, pharmacodynamic and pharmacokinetic principles.

8. The registration dossier must provide a complete rationale of:

the physical form of the modified release product and the mechanism of the release;

the choice of the dosage form, describing the *in vitro* and *in vivo* performance of the product;

the choice of active substance contents per unit of the dosage form;

the clinical rationale for the new dosage form, particularly in relation to the proposed indications and posology.

1. Clinical Rationale

9. A prolonged release dosage form may be acceptable if the active substance is able to produce the desirable clinical effect with a different pharmacokinetic profile than that produced with an immediate-release form administration. A prolonged release dosage form may offer a number of advantages over an immediate-release dosage form. For example:

reduced fluctuations in product plasma concentrations, which may provide more long-lasting effects and (or) reduced incidence and (or) intensity of adverse reactions;

lower frequency of administration and potentially improvement of responsiveness by patients;

other then oral route of administration (intramuscular, subcutaneous, or using transdermal patches).

10. A biphase modified release formulation may be appropriate if a rapid onset of action is required in addition to subsequent prolonged release.

11. The development of a delayed release dosage form may be appropriate to protect the active substance from the acid environment of the stomach, to protect the stomach from the active substance, or when the active substance is intended to be released in a defined segment of the intestine.

12. The development of a pulsatile release dosage form may be appropriate when treatment needs to be adjusted to a daily (circadian) rhythm of the underlying condition or when lower frequency of dosing is required, but the fluctuating plasma concentration profile, which is a characteristic of the immediate-release formulation, is necessary for efficacy.

2. Issues on use and posology

13. The conditions of administration of the modified release dosage form and, where appropriate, its use in conjunction with an immediate release dosage form should be clearly outlined in the following cases:

at the beginning of treatment; when dose titration is required; for maintenance of therapeutic effect; in the treatment of acute diseases;

in special populations such (the elderly, children, and patients with renal or hepatic insufficiency).

Lack of dose strengths of the modified release form to cover all required dose levels (for example, a lower dose for special populations) should be rationalized.

When appropriate, recommendations should be given for replacing immediate release dosage forms to modified release dosage forms. If applicable, specific recommendations should be provided to ensure optimum conditions of use (for example, instructions not to chew or crush tablets).

IV. Studies of modified release dosage forms containing new chemical entities as active substances

14. If a new chemical entity is included as an active ingredient in composition of a modified release product under development, the registration dossier should contain the appropriate pharmaceutical and chemical data, necessary preclinical studies and a complete clinical data package.

1. Pharmacokinetic studies of oral medicinal product with modified release of a new chemical entity

15. A complete pharmacokinetic data package is required for a new chemical entity developed as an active ingredient in a modified release product composition. Additional documentation specific to the modified release dosage form include studies evaluating factors affecting the biopharmaceutic performance of the modified release formulation (see subsection 1, section V).

16. In order to avoid a duplication of studies (for example, dose and time dependence), it is recommended to conduct pharmacokinetic studies with the modified release dosage form as early as possible during clinical development. Initial studies of phase I development (for example, first-in-

human studies) are conducted with an oral solution or an immediate release product where basic pharmacokinetic characteristics of an active substance (tmax, Vd, Cl, terminal elimination half-life, route(s) of excretion) are obtained. Studies of medicine interaction and studies in special populations should preferably be conducted with the modified release product. In addition to general pharmacokinetic studies required for any new medicinal product (e.g. the determination of pharmacokinetic features with single and multiple doses, and when relevant food effect and dose proportionality), the mechanism for the control of active substance release should be described. This is, as a rule, done during the bioequivalence studies (relative bioavailability), conducted using different formulations where, for instance, the amount of an excipient that control the release varies. If possible, the obtained pharmacokinetic profiles *in vivo* are recommended to be compared with the release profiles of the active substance *in vitro* (Addendum 2).

Food effect studies on oral modified release dosage forms

17. Food interactions may be due to the active substance or the product, the latter is most important for the modified release medicinal products.

18. The optimal experimental conditions for the study of food effect include the ingestion of a very fat meal immediately before product intake (see subsection 1, section V).

19. Food effect studies for new modified release medicinal products are recommended to be conducted at an early stage of development so that appropriate recommendations regarding intake in relation to food can be included in clinical efficiency and safety studies. This is also important for safety reasons, as the prospective risk of rapid dose release should be evaluated before initiation of efficiency and safety studies.

20. To evaluate the influence of food on the absorption of the active substance from the new medicinal product a cross-over study in two groups (intake of a modified release medicinal product under fasting and fed conditions) sometimes may be sufficient. If there is a clinically significant effect of food on the modified release medicinal product additional study (ies) with an oral solution may be required, to evaluate if the food effect is related to the medicinal product, dosage form or to active substance. In this case, a cross-over study in four groups may be conducted: A modified release medicinal product under fed and fasting conditions compared to an oral solution with (or an immediate release product if to use a solution is not possible) fed and fasted.

21. In the presence of clinically significant effects of food for the development of dosing recommendations, additional food-interaction studies might be needed, for example, studies of the effect of different kinds of food relative to its calorific value and composition, aimed at establishing the effect of food consumed during certain periods of time before and after taking the medicinal product, etc.

Pharmacokinetic Studies of Transdermal Patches

22. If a new chemical entity is developed to be administered in a transdermal patch formulation, the registration dossier should contain the appropriate pharmaceutical and chemical data and a necessary non-clinical and clinical studies, and as a complete package of clinical data.

23. In general, the kinetics of active substance delivery from transdermal patch is determined by the interaction between the active substance, product excipients and the skin. *In-vitro* and *in-vivo* studies should be conducted to evaluate the diffusion characteristics of the active substance and the rate limiting step, which determines systemic

bioavailability (for example, the release and (or) the accumulation of skin active substance), and (or) other relevant properties of the medicinal product. Pharmacokinetic studies should comprise single-dose and multiple-dose studies considering particular aspects, for example:

application site-dependent absorption;

concentration fluctuation;

latent period;

«concentration-time» profile after transdermal patch removal.

To establish *in vitro* and *in vivo* correlation (IVIVC) is advisable. In the case of the development of several dose strengths, dose proportionality issues should be adequately investigated (subsection 1, section V).

24. In addition to standard phase I studies, the following should be investigated:

skin irritation;

sensitization (see Addendum 1);

phototoxicity and adhesiveness of transdermal patch (see Addendum 4).

When assessing patch adhesion, the influence of external factors (for example, temperature, sun cream) should be considered. As a rule, transdermal patches are designed to deliver the active substances to elderly people. Therefore, tests should be performed in individuals with skin condition similar to the expected skin condition in patients. The Instruction on Medical Application (the Product Information Leaflet) to medicinal product should provide specific instructions on the use in special situations (for example, in sauna). To avoid errors related to the use of transdermal patches (for example, due to poor visibility), the development of invisible patches should be considered conservatively. In such cases the application of

prominent ink as printing on the patches to increase visibility is recommended.

3. Pharmacokinetic studies required for intramuscular (subcutaneous) depot formulations

25. The kinetics of intramuscular (subcutaneous) depot formulations is determined by the interaction between the active substance of the product and muscle tissue. *In-vitro* and *in-vivo* studies should be performed to evaluate diffusion characteristics of the active substance from the intramuscular (subcutaneous) depot formulation and the rate limiting step that determines systemic bioavailability, for example, release of active substance from the skin reservoir and (or) the circumstances mediated by the product. Pharmacokinetic studies should include single-dose and multiple-dose studies considering particular aspects (for example, application site-dependent absorption, concentration fluctuation, latent period). To establish *in vitro* and *in vivo* correlation (IVIVC) is recommended. In case of several dose strengths, dose proportionality issues should be adequately investigated.

V. Study of a modified release dosage form the active substance of which is authorized to be marketed in a formulation with a different release rate

26. Modified release dosage forms are developed based on the current correlation between the pharmacological and toxicological response and the characteristics of systemic exposure to the active substance and (or) metabolite(s). Therefore, the purpose of the modified release dosage form is, in most cases, to reach a total exposure (AUC) of active substance similar to that of an immediate release dosage form. This is not necessary that the same nominal doses are used as the modified release dosage form may have a different extent of absorption or metabolism.

27. In general, modified-release dosage form are not bioequivalent to their respective immediate release dosage form. Consequently, the use of pharmacokinetic data alone may not be sufficient to evaluate the benefit/risk ratio of the modified release dosage form, compared to the corresponding doses of the immediate release dosage form. In the absence of other rationale, additional clinical data referred to in subsection 2, section V are generally required.

28. In the case where the strength of the new modified release dosage form differs from the strength authorized to be marketed for the immediate release dosage form this difference and the possible following different dosage regimen has to clearly indicated in the Summary of Product Characteristics, the Product Information Leaflet and labelling information as most important routine risk minimization measures to prevent application errors. The applicant has to prove that the benefits of the new dosage form outweigh the potential risks linked with this product (for example, improper use).

29. The new product should be characterized in appropriate single dose and multiple dose pharmacokinetic, pharmacodynamic and clinical studies of efficiency (safety). In some cases, additional studies may be required (for example, pharmacokinetic studies may be necessary to characterize the metabolic profile if a modified release dosage form is administered by a new route of administration).

30. Toxicological, pharmacological or clinical tests to define the essential properties of the active substance are not required assuming that modified release formulation and immediate release formulation lead to a similar total exposure of the active substance (metabolites).

31. The immediate release product that is authorized to be marketed with the same active substance should considered as the reference product.

The reference market formulation should in general be used in the pharmacokinetic and therapeutic studies, until it is established that differences between the reference and study products do not affect release characteristics and bioavailability.

1. Pharmacokinetic studies

32. The purpose of pharmacokinetic studies is to characterize the modified release dosage form *in vivo* by determining:

rates and extent of absorption;

concentration fluctuations of the active substance at steady state;

inter-subject variability in pharmacokinetics arising from the product formulation;

dose proportionality;

factors affecting the performance of the modified release dosage form;

the risk of unexpected release characteristics (for example, fast dose release).

33. The studies are based on concentration measurements of the active substance and (or) metabolite(s), and in some cases, in conjunction with determination of an acute pharmacodynamic effect. Due to the significant influence of the composition of the medicinal product requirements for metabolites given in the Rules for Conducting Bioequivalence Studies of Medicinal Product within the Eurasian Economic Union (hereinafter – the Rules for Conducting Bioequivalence Studies of Medicinal Product) is not applicable in this case. The concentration of metabolites should be measured since a change in absorption rate or route of administration may modify the extent and route of metabolism.

34. The studies should be performed either in healthy volunteers or in patients in case of safety concerns.

35. When multiple dose studies are performed, it should be demonstrated that steady state has been reached. Achievement of steady-state, in the absence of other rationale, is assessed by comparing at least three pre-dose concentrations before administration of each dose of the medicinal product. In case of no accumulation multiple dose studies are not required (i.e. insignificant levels at the end of the dosing interval) based on the criteria outlined in subsection 1, section VI.

36. In terms of concomitant food intake, the multiple dose bioavailability study under the conditions stated in the Summary of Product Characteristics, until the steady state is reached, should be performed. If the Summary of Product Characteristics defines a certain timing of food intake in relation to product administration, this time period should be used throughout the study, including the day of determination of pharmacokinetic profiles. If the Summary of Product Characteristics recommends intake of the medicinal product under fasting condition (without specifying time frames) or irrespective of food intake, a worst-case fasted condition (for example, overnight fast and within 4 hours fast after dose intake) should be used on the day of determining the pharmacokinetic profiles. If the Summary of Product Characteristics recommends intake under fed conditions normo-caloric meals should be used throughout the study including the days of determination of pharmacokinetic profiles unless different meal conditions are defined in the Summary of Product Characteristics.

Rate and extent of absorption, fluctuation

37. Rate and extent of absorption of the active substance from a modified release dosage form should be evaluated by comparison with an

immediate release dosage form following single dose administration and if there is cumulation also following repeated dose administration. The studied pharmacokinetic parameters may include:

a) for single dose studies:

$AUC_{(0-t)}$;

$AUC_{(0-\infty)}$;

residual area;

C_{max};

t_{max};

$t_{1/2}$;

t_{lag},

b) for multiple dose studies:

$AUC_{(0-t)}$;

$t_{max,ss}$;

$C_{max,ss}$;

$C_{min,ss}$;

concentration fluctuation.

The pharmacokinetic parameter(s) chosen as primary for the comparison, i.e. the parameter considered as the most likely to reflect efficacy and safety should be rationalized.

38. It should be demonstrated that the modified release dosage form has the claimed release characteristics. It is recommended to employ deconvolution of the «concentration – time» data for the modified release dosage form compared to the corresponding immediate release dosage form in order to obtain the cumulative absorption (or *in vivo* release) profile versus time profile for the modified release dosage form. Cumulative absorbed quantities and rate of absorption versus time should be used to support the claimed release characteristics.

39. After repeated administration of the dose, it is necessary to investigate the fluctuation in the concentration of the active substance. Unless otherwise rationalized, the modified release dosage form should show similar or less fluctuations compared to the immediate release dosage form.

40. If the modified release dosage form is to be administered to patients already treated with an immediate release dosage form (change in the administration of the dose, switching), the specific dosing instructions during the switch should be considered to maintain steady state concentrations.

Dose levels and strengths to be evaluated

41. If the active substance and the modified release dosage form exhibit linear pharmacokinetic properties it may be sufficient to compare the modified release dosage form and the immediate release dosage form after single and, in case of product accumulation, after multiple dose administration at one dose level.

42. If the active substance or the modified release dosage form exhibit nonlinear pharmacokinetics (in the therapeutic plasma concentration range) it is necessary to compare the modified release dosage form and the immediate release dosage form at least at the highest and the lowest dose level. If the immediate release and modified release dosage form display different extent of non-linearity, additional strengths may need to be compared.

2. Variability

43. In single and multiple dose studies described in subsection 1, section V, it is necessary to determine the inter-individual variability of the pharmacokinetic parameters of interest and compare them between the modified and immediate release dosage forms. The variability for the modified release dosage forms should preferably not exceed that for the

immediate release dosage forms unless it is adequately rationalized in terms of potential clinical consequences.

3. Dose proportionality

44. If there are several strengths or if several single units can be taken simultaneously to achieve the desired dose, dose proportionality for different strengths (doses) of the modified release dosage form should be adequately investigated. Dose proportionality should be evaluated by means of a single dose and, in case of the active substance accumulation, a multiple dose study, where the pharmacokinetic parameters of interest of all the strengths (doses) are compared after dose adjustment. In this case, the dose proportionality criteria given in the Rules for Conducting Bioequivalence Studies of Medicinal Product based on the AUC and 25% acceptance range are not applicable, since they are applicable only to the strength selection in bioequivalence studies.

4. Factors affecting the performance of a modified release dosage form

Food

45. The influence of food on the bioavailability of modified release dosage forms should be investigated in a single dose study. The optimal experimental conditions for obtaining a food effect include the ingestion of a pre-defined high-fat high-calorie meal immediately before dosing. It is recommended that subjects should start the meal 30 minutes prior to administration of the medicinal product and finish this meal within 30 minutes. The meal should be high-fat (approximately 50 percent of total caloric content of the meal) and high calorie (approximately 800 to 1000 kcal). The meal used for test should contain approximately 150, 250, and

500-600 kcal of protein, carbohydrate and fat, respectively. The composition of the meal should be described with regard to protein, carbohydrate and fat content specified in grams, absolute and relative (percentage) caloric content.

46. The design of the food effect study depends on other studies performed which compared the modified release dosage form with the immediate release dosage form and if there is a clinically significant food effect on the immediate release dosage form.

47. If there is no clinically relevant food effect on the immediate release dosage form, a two-way cross-over study comparing the modified release dosage form under fasted and fed conditions may be sufficient provided that other studies compare the modified release and the immediate release dosage forms under fasted conditions.

48. In the presence of clinically significant food effects for the immediate release dosage form, a crossover study in four groups comparing the modified release dosage form under fasting and fed conditions and the immediate release dosage form under fasting and fed conditions could be useful to quantify the food effect on each dosage form.

49. If there are several strengths, the food effect can be investigated for one of the strengths only if the products are proportional in composition (for example, multi-particulate dosage forms or proportional tablets based on composition), have the same manufacturing process, exhibit linear pharmacokinetics and their dissolution profiles are similar in a range of dissolution media. The highest strength should be tested, unless otherwise rationalized. In case the above conditions are not fulfilled, it is necessary to investigate the food effect at the highest and the lowest strengths or the extreme conditions based on a bracketing approach.

50. For the assessment of food effect in addition to AUC and C_{max}, it may also be advisable to compare the modified release characteristics by verifying that the shape of the «concentration – time» profiles are not significantly changed.

51. The clinical significance of the food effect should be discussed from both an efficacy and a safety perspective. When needed, dose recommendations with respect to intake of the product in relation to meals should be given. To rationalize the recommendations for dosing, additional studies with another type of food or when taking the product at certain intervals before and after eating may be required.

52. If the formulation or the manufacturing process is changed during medicinal product development in a way that potentially affects release characteristics, a new evaluation of the food effect for the final product may be required.

53. In the medicinal product information of certain multiple unit dosage forms, it may be recommended that the product may be opened and pellets (granules), for example, may fall into soft foods, be dispersed in a glass of still water and swallowed without chewing or administration through the gastric probe. In order to add an indication of such an additional method of administration, additional stability and dissolution tests *in vitro* should be carried out to confirm the equivalence between the unopened and the opened dosage form. The absence of bioequivalence studies imitating the additional options of administration should be rationalized.

Gastro-intestinal function

54. If an oral modified release dosage form is usually expected to be co-administered with active substances affecting gastrointestinal physiology

(for example, opioids) it is necessary to investigate the performance of the oral modified release dosage form under these conditions.

55. If the oral modified release dosage form is intended for patients with severe gastrointestinal disfunction the modified release dosage form may need to be studied also in those patients.

Unexpected release characteristics

56. Unintended, rapid release of the entire amount or a significant portion of the active substance contained in a modified release dosage form is often referred to as «rapid dose release» (“dose dumping”). Depending on the therapeutic indication and the therapeutic range of an active substance, dose-dumping may pose a significant risk to patients in terms of reduced safety, reduced efficiency, or both.

57. It is necessary to exclude the risk of unexpected release resulting in unforeseen exposure of modified release dosage forms. If dose dumping is observed (for example, a significantly higher maximum exposure with an inappropriate modified release profile) or suspected (for example, absence of concentration of a labile active substance in gastro-resistant formulation for some subjects) the product formulation should be re-developed to avoid this deficiency of the biopharmaceutical quality.

58. A higher maximum exposure might also be observed in prolonged release products due to active substance release in the stomach for an extended period of time (for example, at delayed gastric emptying) followed by absorption of the released dose only after emptying the stomach contents. Since such an unexpected increased exposure is not related to a particular product failure causing uncontrolled release, dosing recommendations with regard to, for example, concomitant food intake should be given to avoid a prolonged residence in the stomach.

Effects of alcohol

59. Some oral modified release dosage forms contain active substances and (or) excipients that exhibit higher solubility in alcohol ethanol solutions than in water. Simultaneous use of alcoholic beverages with such products may lead to dose dumping. For such dosage forms, *in vitro* studies of the release in alcohol solutions should be performed. If accelerated active substance release is seen *in vitro* at either high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the composition of the dosage form should be reformulated. Only if there is a justification that the interaction with alcohol *in vitro* cannot be prevented by changing the composition of the dosage form, it is acceptable to conduct an *in vitro* study to confirm that such interaction *in vivo* is unlikely to occur.

60. The *in vivo* investigation of alcohol-induced dose-dumping should compare the systemic exposure when the modified release dosage form is ingested with a reasonable amount of alcohol on an empty stomach. The results of this study should be evaluated not only with respect to the clinical significance of changes in the group mean, but also the clinical consequences for the observed individual ratios.

61. If there is a high probability of a significant dose-dumping effect *in vivo*, which cannot be avoided by changing the composition of the dosage form, it is necessary to carefully evaluate the «benefit/risk» of the product. Indication of alcohol use in contraindications is not an appropriate measure to prevent product-alcohol interaction. Information on appropriate interactions with alcohol, if it leads to clinically significant potentiation or harmful additive effect should be given in the product information. In addition, the need for other precautionary measures and risk management strategies should be analyzed.

5. Other factors to consider

Special populations

62. Different physiological conditions (for example, transit times, pH, food intake and type of food) in vegetarian, pediatric and elderly patients or in patients routinely taking antacids should be taken into consideration especially when designing oral once daily modified release medicinal products.

Influence of site of injection (application) on plasma concentration

63. It is necessary to investigate the effect of different sites of subcutaneous (intramuscular) depot formulations or applying transdermal patches on the absorption of the active substance, if this site is not limited to one area of the body, the safety and tolerability of these dosage forms at the site of injection (application) should be evaluated.

64. It is necessary to make sure that not only the plasma concentrations of subcutaneous (intramuscular) depot formulations or transdermal patches are within the therapeutic range at the end of the dosing interval, but also to investigate how the plasma concentration decreases after removal of the depot formulation or transdermal patch.

Multiphase modified release formulations

65. There are modified release dosage forms that have been developed solely in order to replicate three or four times daily dosing regimen. In these cases the «plasma concentration – time» profile of the modified release dosage form should be equivalent with the immediate release dosage form given in the dose regimen that is imitated unless comparable efficiency and (or) safety is confirmed by additional clinical data.

Prolonged gastric residence time

66. Gastric emptying from single unit dosage forms that do not disintegrate in the stomach may be prolonged and unstable. The consequences of this effect on the enteric coating of delayed release dosage forms are largely unpredictable. If an acid labile active substance release occurs prior to stomach emptying, degradation of the active substance can be caused and non-existing «plasma concentration time» files can be obtained. In addition, the release of the active substance may be significantly delayed due to a prolonged residence in the stomach. Therefore, the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but also the possible occurrence of this effect to make sure that effect of delayed gastric emptying is properly characterized.

2. Therapeutic studies

67. Unless adequately rationalized, the comparative clinical efficiency and safety data are required to provide in addition to pharmacokinetic data during the process of the development of modified release dosage forms after the development of the immediate release dosage forms. Since the efficiency and safety of the immediate release dosage form is known, the major issue would be to demonstrate that the new modified release dosage form is as safe and effective as the existing one. Additional benefits of the new dosage form should be supported or rationalized.

68. However, in exceptional cases, if the assessment of «concentration-effect» relationship indicates that there is a well-defined relationship between plasma concentration of the active substance (active metabolite(s)) and clinical response, clinical trials may be considered unnecessary. In this

case, the same or a better level of efficiency and safety may be established as a result of pharmacokinetic studies (pharmacodynamics).

69. When assessing pharmacokinetic (pharmacodynamic) relationships for modified release dosage forms, the differential effects on efficiency and safety due to differences in rate of absorption and fluctuation should be evaluated. It is important not only to establish «concentration – effect» relationships, but also to determine the significance of differences in the shape of «the steady state concentrations – time» profile for a regimen with modified release dosage form administration as compared to the regimen with immediate release dosage form that is authorized to be marketed. Tolerance to therapeutic effects and toxic effects due to exposure, concentration, absorption rate and fluctuation of the active substance should also be investigated.

Waiving of therapeutic studies

70. Therapeutic studies may not be performed if at least one of the following conditions is met:

bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ because the new modified product is developed to mimic the performance of product with a different release mechanism and its dosage regimen (for example, a pulsatile multi-phase release dosage form containing pellets (granules) with different release time);

bioequivalence between the reference and the test product is shown in terms of $C_{max,ss}$, $C_{min,ss}$ and $AUC_{(0-\tau)ss}$ despite differences in the shape of «the plasma concentration-time» profile if it is possible to rationalize that the difference in shape has no relevance for efficiency and safety based on «the exposure – response» relationships and «shape – response» profile;

there is a well-defined therapeutic window in terms of safety and efficiency, the rate of input is known not to influence the safety and efficiency profile or the risk for tolerance development and bioequivalence between the reference and the test product is shown in terms of $AUC_{(0-\tau)ss}$ and $C_{max,ss}$ for the new modified release dosage form is below or equivalent to the $C_{max,ss}$ for the authorized dosage form whereas $C_{min,ss}$ for the modified release dosage form is above or equivalent to the $C_{min,ss}$ of the registered dosage form.

Clinical study designing

71. Comparative studies should be adequately designed and conducted to assess the intensity and duration of the therapeutic effect and undesirable effects of the modified release dosage form in comparison with the immediate release dosage form that is authorized to be marketed. Studies should establish the clinical benefit of the new product relative to the immediate release product that is authorized to be marketed, if such properties are claimed. In addition to specific guidelines the following factors should be considered:

in the assessment of the efficiency and safety of certain therapeutic classes it is necessary to determine the effects of the product throughout a 24-hour period and particularly at the end of dosage interval (for example, assessment of breakthrough of uncontrolled pain);

the different effects of medicinal products having different dose thresholds:

therapeutic activity is quantitatively evaluated with reference to the pharmacodynamic or clinical effects normally adopted as criteria for the assessment of efficiency in the concerned therapeutic class;

in exceptional cases only, where the mechanism of action is the same between different indications, an extrapolation may be made based on the uninvestigated indications, if it is appropriately rationalized by the applicant;

in cases when the prolonged therapeutic activity may worsen the safety profile of the medicinal product during chronic dosing, safety studies may be required.

72. Clinical trials which compare the modified release dosage form and the immediate release dosage form based on equal exposure may be performed to demonstrate non-inferiority of therapeutic efficiency or equivalence. In any case, the recommendations of the guidelines on the principles of application of biostatistics in clinical trials adopted by the Eurasian Economic Commission should be taken into account in the design and analysis of trials.

73. The ability of pharmacodynamic (clinical) studies to show equivalence or non- inferiority of efficiency compared to the reference dosage form depends on the direction of the effect or safety issue. In case efficiency and safety are closely related, equivalence studies are needed for showing that the effect studied remains within the equivalence range. If it is acceptable to investigate only efficiency and dosage forms are not expected to have different safety, a demonstration of non-inferiority might be sufficient.

74. The type of studies that are required depends on the possibility to determine the appropriate pharmacodynamic endpoints, data on the relationship between pharmacodynamic markers and clinical efficiency, and on the possibility to guarantee assay sensitivity and on the possibility to determine a non-inferiority limit of efficiency and equivalence.

75. Such equivalence and non-inferiority studies except for the immediate and modified release medicinal products may include a placebo

arm. A placebo arm or an additional active arm with a lower dose is mandatory to include if assay sensitivity of the trial cannot be guaranteed.

76. In addition, equivalence limits or non-inferiority limits should be defined and rationalized irrespective of whether the endpoint is based on pharmacodynamic marker or clinical variable.

77. It is necessary to compare the design of clinical studies, corresponding to the current guidelines or the current state of the art, if the claimed indication for the modified release product is different from that of the immediate release product. In case the modified release product is either a patch or a depot formulation, the safety of local administration should also be investigated.

78. The remaining amount of active substance after patch removal should be considered in respect to potential misuse or environmental risks.

79. The claimed superiority of the modified release dosage form should be demonstrated in clinical studies. Applicants should refer to the scientific guidance documents in the relevant therapeutic area.

80. The claimed fewer systemic adverse reactions for the modified release form should be rationalized.

VI. Modified release dosage forms compared to the authorized modified release dosage form

1. General provisions

81. For orally administered dosage forms, bioequivalence studies are recommended to be conducted by comparing two similar dosage forms (test versus reference). A generic modified release product should be compared with the modified release product that is either the originator or the line extension of an immediate release originator in relation to which

bioequivalence is claimed. The general recommendations regarding study design, conduct, evaluation and reporting of bioequivalence studies given in the main text of the Rules for Conducting Bioequivalence Studies of Generic Medicinal Products are also applicable to studies of bioequivalence of modified release dosage forms. Specific aspects for modified release dosage forms are given in this section.

82. If two products with the same dosage form differ in their excipients or mechanism of release controlling they can be considered generics if they are bioequivalent *in vivo* after single dose under fasting and fed conditions and, if necessary, after repeated administration.

83. If the biowaiver criteria for additional strength are met and bioequivalence demonstration is required only for one strength of the product, the following is recommended:

if the pharmacokinetics of the originator modified release product are linear, single and multiple dose studies should be conducted at the highest strength;

if the pharmacokinetic of the originator modified release product are nonlinear the studies should be conducted with the most sensitive strength. Safety considerations should be taken into account when choosing a lower dose.

84. As a rule, studies are conducted with the participation of healthy volunteers. If it is not possible to conduct studies in healthy volunteers in any existing strength due to safety reasons, studies can be conducted in patients, preferably after both single and multiple dose administration in accordance with the recommendations below. If it is unacceptable to conduct study in patients, these may be replaced by multiple dose studies.

85. In case criteria for bracketing approach are fulfilled and the demonstration of bioequivalence is needed for two strengths selected to represent the extremes the following recommendation is given:

the study with the highest strength of the product in patients and the study with the lowest strength of the product in healthy volunteers;

the evaluation of dissolution profiles, pharmacokinetic linearity and determination of the most sensitive strength of the product is carried out in accordance with the main text of the Rules for Conducting Bioequivalence Studies of Generic Medicinal Products within the Eurasian Economic Union.

86. Differences due to the product-food interaction, indicate differences contradicting the generic by definition. If the bioequivalence of the product is demonstrated under the conditions recommended in the Summary of Product Characteristics, but not under the non-recommended conditions due to less food effect, the product does not meet the requirements for the generic product but may meet the criteria for authorization as a hybrid medicinal product.

2. Prolonged release products for oral administration

87. Bioequivalence between two prolonged release products should be evaluated on the basis of studies designed to demonstrate that:

the test product exhibits the claimed prolonged release characteristics of the reference product;

the active substance is not released unexpectedly from the test formulation (no dose dumping);

performance of the test and the reference product is equivalent after single dose and at steady state;

the effect of food on the *in vivo* performance is comparable for both products when a single dose study is conducted.

Studies normally required to demonstrate bioequivalence

88. The following is required to demonstrate bioequivalence:

a single dose study of test and reference products product under fasting condition;

a single dose study of test and reference products under fed conditions using a high-fat meal;

a multiple dose study of test and reference products.

Single dose studies

89. One of the following schemes is recommended for single dose evaluation under fasting and fed conditions:

a four-period cross-over study with four complementary sequences of four treatment conditions. Both the test and reference products should be assessed in the fasting state as well as after the administration of a high-fat meal at a specified time before taking the product;

two cross-over studies. The first study should compare the test and reference products under fasting conditions. The study products should be administered during two periods and with two sequences of treatment conditions. The second study should compare the test and reference products following the administration of a high-fat meal at a specified time before taking the test products, as well as the test product under fasting conditions in order to generate individual data characterizing a possible food effect;

two cross-over trials, both with two periods and two sequences of test and reference product administration. One study should be conducted under fasting condition. The second study should be conducted after the administration of a high-fat meal at a specified time before taking the test product.

Multiple dose studies

90. A multiple dose study should be conducted unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference, and therefore a large accumulation (cumulation) is expected. In this case bioequivalence should be demonstrated for additional parameters representing the shape of the «plasma concentration – time» curve in the single dose study (see also subsection 9.2, section VI). It is recommended to investigate the initial $_{partial}AUC_{(0–cut\text{-}off\ t)}$ and a terminal $_{partial}AUC_{(cut\text{-}off\ t\text{-}tlast)}$, separated by a predefined cut-off time point, for example, the half of the dosage interval are recommended, unless otherwise scientifically justified.

In all other cases, where the probability of accumulation (cumulation) is ($AUC_{(0-\tau)}$ after the first dose covers less than 90% of mean $AUC_{(0-\infty)}$) a multiple dose study should be conducted. In general, steady-state studies should be performed under the conditions that reflect concomitant food intake in accordance with the Summary of Product Characteristics of the originator product. If the Summary of Product Characteristics states that the product has to be taken under fed condition the study should be performed only under fed condition (standard meal), including the day of determination of the profile. If the Summary of Product Characteristics states that the product should be taken under fasting condition or irrespective of food intake the studies should be performed under fasting condition. Fasting conditions in a multiple dose study should be adapted to realistic situations, for example, morning administration requires a 10-hour fasting interval whereas for all other administrations 4-hour fasting prior to administration is sufficient. Fasting after each administration should last at least 2 hours.

91. In steady-state studies, the washout period after the previous product may be overlapped by the addition of a second product concentration (direct switching), provided the addition period is sufficiently long (at least 5 times the terminal half-life). The achievement of the steady-state is assessed by comparing at least three dose concentrations for each product before the next administration. The apparent half-life should also be taken into account.

Strength(s) to be evaluated

Single unit products

92. For single unit products with multiple strengths the following principles apply:

1) in single dose studies: if the Summary of Product Characteristics of the reference product recommends intake under fasting condition or irrespective of food intake:

a single dose study under fasting condition is required for all strengths under fasting condition. However, a bracketing approach is also possible if rationalized. For the safety of healthy volunteers, studies should be conducted in patients, which may require steady state conditions; one single dose bioequivalence study at the highest (most sensitive) strength conducted under fed condition may be sufficient. The other strengths may be waived if the biowaiver strength criteria described in subsection 7 of section III of the Rules for Conducting Bioequivalence Studies of Medicinal Products within the Eurasian Economic Union is met. However, if the strengths of the test product do not meet these criteria or if the different strengths have different shape two strengths representing the extreme difference should be tested under fed condition;

2) in single dose studies: if the Summary of Product Characteristics of the reference product recommends intake under fed conditions:

a single dose study under fed conditions is required for all strengths. However, a bracketing approach is also possible if rationalized;

one single dose bioequivalence study at the highest (most sensitive) strength conducted under fasting condition may be sufficient. The other strengths may be waived if the biowaiver strength criteria described in subsection 7 of section III of the Rules for Conducting Bioequivalence Studies of Medicinal Products is met. However, if the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the extreme difference should be tested under fasting condition.

93. A multiple dose study should be performed with the highest strength (unless it is shown that there is no accumulation (cumulation)). For safety reasons, the study should be conducted in patients. Other strengths may be waived if the biowaiver strength criteria described in subsection 7 of section III of the Rules for Conducting Bioequivalence Studies of Medicinal Products is met. However, a bracketing approach is also possible if rationalized (subsection 7 of section VI).

Multiple unit products

94. For several strengths of multiple unit products, it is sufficient to conduct the studies listed in subsection 1 of section VI of this Guide only at the highest (most sensitive) strength if the compositions of the strengths are proportional, the formulations contain identical pellets (which are produced by the same manufacturing process) and the dissolution profiles are similar.

3. Delayed release products

95. Bioequivalence between two delayed release medicinal products should be evaluated on the basis of studies designed to demonstrate that:

the test product exhibits the claimed delayed release characteristics of the reference product;

the active substance is not released unexpectedly from the test product (to ensure the targeted location of release);

the performance of the test and the reference products is equivalent after a single dose;

the effect of food on the *in vivo* performance is comparable for both products in a single dose study.

Studies normally required to demonstrate bioequivalence

96. As a rule, the following is required to demonstrate the bioequivalence:

a single dose study of the test and reference products under fasting condition;

a single dose of test and reference products under fed condition of the high-fat meal.

When designing single dose studies, it is possible to apply an approach similar to that for prolonged release dosage form.

Strength(s) to be evaluated

Single unit products

97. In single dose studies of single unit products: if the Summary of Product Characteristics of the reference product recommends its intake under fasting condition or irrespective of food intake: A single dose study under fasting condition is required for all strengths under fasting condition. A bracketing approach is also possible if rationalized. One single dose bioequivalence study at the highest (most sensitive) strength conducted under fed condition may be sufficient. The other strengths may be waived if the

biowaiver strength criteria described in subsection 7 of section III of the Rules for Conducting Bioequivalence Studies of Medicinal Products is met. If the strengths of the test product do not meet these criteria or if the different strengths have different shape two strengths representing the extreme difference should be tested under fed condition.

98. In single dose studies of single unit products: if the Summary of Product Characteristics of the reference product recommends its intake only under fed conditions: A single dose study under fed conditions is required for all strengths. However, a bracketing approach is also possible if rationalized. One single dose bioequivalence study at the highest strength conducted under fasting condition may be sufficient. The other strengths may be waived if the biowaiver strength criteria described in subsection 7 of section III of the Rules for Conducting Bioequivalence Studies of Medicinal Products is met. If the strengths of the test product do not fulfil these criteria or if the different strengths have different shape two strengths representing the extreme difference should be tested under fasting condition. When evaluating proportionality in composition, the similarity of gastro-resistant coating with respect to the surface area (not to core weight) should be considered to have the same gastro-resistance (coating layer in mg/cm^2 of the surface).

99. In principle there is no need for multiple dose studies except for the cases when single dose studies cannot be performed due to safety reasons (see also subsection 1, section VI).

Multiple unit products

100. For several strengths of multiple unit products, it is sufficient to conduct the studies listed in subsection 3 of section VI of this Annex only at the highest (most sensitive) strength if the compositions of the strengths are

proportional, the formulations contain identical pellets (which are obtained by the same manufacturing process) and the dissolution profiles are similar.

Prolonged residence time of dosage forms in the stomach

101. Gastric emptying of modified release dosage forms that do not disintegrate in the stomach (for example, enteric coated tablets) may be prolonged and highly variable. The consequences of this effect on the enteric coating of delayed release products are largely unpredictable and can result in non-existing or abnormal concentration profiles. If such abnormal behavior is observed with a comparable frequency (for example, the number of cases in the study group does not exceed the number of cases in the reference group) in both, test and reference product groups, data on time periods with a non-existent or abnormal profile can be excluded from the statistical analysis provided it has been pre-specified in the study protocol. In a two-period study, this implies excluding the subject from the analysis. If the percentage of excluded subjects exceeds 20% for a particular study, the validity of the study may need to be verified.

In addition, the release of the active substance may be considerably delayed due to a prolonged residence in the stomach. Therefore, the sampling period should be designed such that measurable concentrations are obtained, taking into consideration not only the half-life of the active substance but also the possible occurrence of this effect.

4. Multiphase modified release medicinal products

102. The regulatory criteria stated in this Annex are also applicable to the assessment of bioequivalence for modified release medicinal products designed to achieve sequential release combining immediate and modified characteristics (for example, biphase (pulsatile) release).

Studies normally required to demonstrate bioequivalence

103. If one of the release phases is modified, the type and number of studies required coincide with those described above for this specific release mechanism. However additional pharmacokinetic parameters should be investigated to demonstrate bioequivalence for all phases.

5. Intramuscular (subcutaneous) depot formulations

Studies required to demonstrate bioequivalence

104. As a rule, the following is required to demonstrate the bioequivalence:

a single dose study of test and reference products;

a multiple-dose study of test and reference products.

A multiple dose study should be conducted unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of mean $AUC_{(0-\infty)}$ for both test and reference products, and consequently a low extent of accumulation (cumulation) is expected.

Strength to be investigated

105. Only one strength has to be investigated if the different strengths are proportional in composition and exhibit a similar *in vitro* dissolution profile. The strength should be selected based on the pharmacokinetic linearity and safety. If there are several non-proportional strengths a bracketing approach is possible, but the formulation strategy of the reference product should be taken into account.

106. If the originator product is authorized to be marketed in only one concentration and the different doses are achieved by choosing the total

volume to be injected, any dose should be acceptable for a bioequivalence study in case dose proportionality has been shown for the reference product. In case therapeutic doses cannot be administered to healthy volunteers, non-therapeutic doses may be acceptable for safety reasons. In situations where it is not possible to perform single dose studies with an intramuscular (subcutaneous) depot formulation in healthy volunteers for safety or ethical reasons, multiple dose studies in patients are acceptable to demonstrate bioequivalence.

6. Transdermal drug delivery system

107. A generic transdermal drug delivery system contains the same amount of active substance released per unit time as compared to the reference transdermal drug delivery system. It should be noted that this definition is different to the general definition of a generic since the overall amount of active substance could differ while the labelled amount of active substance released per unit time should be the same between a generic and the original transdermal drug delivery system.

The study of the equivalence of transdermal systems should show comparable or higher adhesive properties and confirm bioequivalence. Comparable or higher adhesion properties should be ensured prior to bioequivalence studies in volunteers since inferior adhesion could invalidate the pharmacokinetic results and question the acceptability of the product. The skin of the population studied in adhesion equivalence testing should also be similar to the population using the medicinal product, which implies that different studies may be necessary for the adhesion and the pharmacokinetic studies.

Studies required to demonstrate bioequivalence

108. As a rule, the following is required to demonstrate the bioequivalence:

a single dose comparative study of test and reference products;

a multiple dose study comparative study of test and reference products.

Bioequivalence of transdermal drug delivery system, as a rule, should be evaluated after a single, as well as multiple doses. A multiple dose study should be conducted unless a single dose study has been performed with the highest strength which has demonstrated that the mean $AUC_{(0-\tau)}$ after the first dose covers more than 90% of the value $AUC_{(0-\infty)}$ for both test and reference products, and a low extent of accumulation (cumulation) is expected. The study design including the site of application should be justified in terms of its sensitivity to detect differences between products. The application site should be standardized. It should be the same for the test and reference products. Due to the change of the patch site application, used for the cross-over, as a rule, another site in the same region is used. The adhesion properties of the patch should not be damaged, for example, due to over-taping for adhesion.

Bioequivalence should be assessed using the same pharmacokinetic parameters and statistical procedures as for prolonged release products.

The test product should demonstrate a similar or lower degree of local irritation, phototoxicity, sensitization, and similar or better adhesiveness to the skin in relation to the reference product. Unless otherwise rationalized, for example, by a very similar quantitative and qualitative composition, in order to ensure equivalence in terms of safety, comparative state-of-the-art studies are required to establish:

cutaneous tolerability, irritation and sensitization;

the possibility to cause a phototoxic reaction;

adhesion characteristics.

Strength to be investigated

109. During the marketing authorization of multiple strengths, a bioequivalence study may be performed with the highest (most sensitive) strength provided that:

the qualitative composition is the same for all strengths;

the strengths are proportional to the effective surface area of the patch and the lower dose strengths can be considered as "partial" areas of the highest dose strength;

there are similar dissolution (release) profiles.

In case of limitations at the highest strength for safety (tolerability) reasons, the use of a lower strength is acceptable for size proportional products.

7. Bracketing approach

110. In case bioequivalence assessment at more than two strengths is needed (for example, if product compositions are not proportional and (or) if dissolution profiles are not similar), or for single unit products with proportional composition, a bracketing approach may be used if the other waiver criteria to perform bioequivalence studies are fulfilled. In this situation it may be acceptable to perform two bioequivalence studies, if the strengths selected represent the extremes, for example, the highest and the lowest strength or the two strengths differing most in composition, dissolution or shape, so that any differences in composition or dissolution in the remaining strengths is covered by the two conducted studies.

However, for prolonged release products, the release control excipients and mechanism should be the same for all strengths of the test product. The same requirements apply to coatings of delayed release products that control release.

8. New strength for a modified release product that is already authorized to be marketed

111. The requirements of section VI of this Annex also apply to the development of a new strength within the dose range described in the Summary of Product Characteristics of the reference product. For a new strength, the composition of which is proportional to the strength(s) that is (are) already authorized to be marketed, a bracketing approach may be applicable. A new strength with non-proportional composition in relation to the strength(s) that is (are) already authorized to be marketed, has to meet the requirements specified in subsections 1 to 6 of section VI of this Annex. If the strength being developed corresponds to the range between the extremes of other strengths and meets the requirements for release control excipients, size (shape) and manufacturing requirements, then a new study should not be required because it falls in the category given in subsection 7, section V of this Annex. A new dose strength which is not included existing therapeutic range requires a clinical development. Certain parameters, for example, skin safety profile for transdermal drug delivery system, may not need to be re-evaluated, if the new strength and the intended indication are not expected to change the overall safety profile.

9. Evaluation

Parameters to be analyzed

112. In single dose bioequivalence studies, it is necessary to determine $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, residual area, $C_{max,}$ t_{max} and, when relevant, $_{partial}$ AUC. A truncated $AUC_{(0-72h)}$ is not acceptable for modified release medicinal products.

113. For multiphase modified release medicinal products additional parameters to be determined include $_{partial}$AUC, C_{max} and tmax in all phases. The time point for truncating the $_{partial}$AUC should be based on the pharmacokinetic profile, for example, of parts of the immediate release and modified released, respectively, and should be rationalized and pre-specified in the study protocol.

114. In studies to determine bioequivalence after a multiple dose administration $AUC_{(0-\tau)ss}$, $t_{max,ss}$, $C_{max,ss}$, $C_{\tau,ss}$, and fluctuation should be determined. In contrast to the need of characterization of $C_{min,ss}$ for new modified release dosage forms, a comparison of $C_{\tau,ss}$, which is easier to determine, should be sufficient. $C_{\tau,ss}$ is required to assess the shape of the curve for generic product and replaces the need to also evaluate $C_{min,ss}$ in these situations.

Evaluation of characteristics and acceptance criteria

115. Bioequivalence for prolonged release products capable of accumulation (cumulation) should be demonstrated after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-\tau)}$, $AUC_{(0-\infty)}$, C_{max};

Multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$.

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of prolonged release products, capable of accumulation (cumulation), is presented in Table 1.

Table 1

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of prolonged release products, capable of accumulation (cumulation)

Pharmacokinetic parameters	Need to estimate the parameters		
	Single dose under fasting condition	Single dose under fed condition	Multiple dose
C_{max}	Yes	Yes	No
$AUC_{(0-\tau)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
$_{partial}AUC$	No	No	No
$C_{max,ss}$	No	No	Yes
$C_{\tau,ss}$	No	No	Yes
$AUC_{(0-\tau)ss}$	No	No	Yes

116. Bioequivalence of prolonged release products with no capability of accumulation (cumulation) or those intended exclusively for once only use, is demonstrated after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty)}$, C_{max} and a representative measurement of the curve shape (for example, early $_{partial}AUC$ and terminal $_{partial}AUC$).

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of prolonged release products, incapable of accumulation (cumulation), is presented in Table 2.

Table 2

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of prolonged release products, incapable of accumulation (cumulation)

Pharmacokinetic parameters	Need to estimate the parameters		
	Single dose under fasting condition	Single dose under fed condition	Multiple dose
C_{max}	Yes	Yes	No
$AUC_{(0-\tau)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
$_{partial}AUC$	Yes	Yes	No
$C_{max,ss}$	No	No	No
$C_{\tau,ss}$	No	No	No
$AUC_{(0-\tau)ss}$	No	No	No

117. Bioequivalence for delayed release products should be demonstrated after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-\tau)}$, $AUC_{(0-\infty)}$, C_{max}.

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of delayed release products is presented in Table 3.

Table 3

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of delayed release products

Pharmacokinetic parameters	Need to estimate the parameters		
	Single dose under fasting condition	Single dose under fed condition	Multiple dose
C_{max}	Yes	Yes	No
$AUC_{(0-\tau)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
$_{partial}AUC$	No	No	No
$C_{max,ss}$	No	No	No
$C_{\tau,ss}$	No	No	No
$AUC_{(0-\tau)ss}$	No	No	No

118. Bioequivalence for multiphase modified release medicinal products should be demonstrated after statistical evaluation of the following parameters:

Single dose: $AUC_{(0-t)}$, $AUC_{(0-\infty),\ partial}AUC$, and C_{max} in all phases;

in the case of accumulation in multiple dose: $AUC_{(0-\tau)}$, $C_{max,ss}$, $C_{\tau,ss}$.

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of multiphase modified release medicinal products is presented in Table 4.

119. The bioequivalence approach considering usual acceptance limits (80,00 to 125,00%) is applicable for generic modified release medicinal products. Any extension of the acceptance criteria for C_{max} should consider the recommendations for highly variable medicinal products in the Rules for Conducting Bioequivalence Studies of Medicinal Product.

Table 4

The need for statistical evaluation of pharmacokinetic parameters in the bioequivalence study of multiphase modified release medicinal products

Pharmacokinetic parameters	Need to estimate the parameters		
	Single dose under fasting condition	Single dose under fed condition	Multiple dose
$C_{max(x)}$	Yes	Yes	No
$C_{max(x+1)}$	Yes	Yes	No
$AUC_{(0-\tau)}$	Yes	Yes	No
$AUC_{(0-\infty)}$	Yes	Yes	No
$_{partial}AUC_{(x)}$	Yes	Yes	No
$_{partial}AUC_{(x+1)}$	Yes	Yes	No
$C_{max,ss}$	No	No	Yes
$C_{\tau,ss}$	No	No	Yes
$AUC_{(0-\tau)ss}$	No	No	Yes

120. The bioequivalence approach considering usual acceptance limits of bioequivalence (80,00 to 125,00%) is applicable for generic modified release medicinal products. Any extension of the acceptance criteria for C_{max} should consider the recommendations for highly variable medicinal products in the Rules for Conducting Bioequivalence Studies of Medicinal Product.

121. A similar approach may be used for extension of the acceptance criteria for $C_{max,ss}$, $C_{\tau,ss}$, and $_{partial}AUC$. Calculation of the intra-subject variability in multiple dose studies may be based on two consecutive administrations of the same product after reaching steady state.

122. For delayed and multiphase release dosage forms differences in t_{max} is also recommended to be assessed, especially for products where a rapid onset of action is important. A formal statistical evaluation of t_{max} is not

required. However, there should be no apparent difference in median t_{max} and its range between test and reference products.

10. Effects of alcohol

123. *In vitro* studies of the release in alcohol solutions should be performed for generic products. If accelerated active substance release is seen *in vitro* either at high or low alcohol concentrations over a short period of time or at lower alcohol concentrations over a longer period of time, the composition of the product should be reformulated. If the alcohol effect cannot be avoided and it is also typical for the reference product, the applicant should rationalize (demonstrate) that it does not have clinical significance or analyse the possible clinical significance for the reference product.

11. Other factors to consider for bioequivalence studies

124. The following factors should be considered in accordance with the recommendations for immediate release products stated in the Rules for Conducting Bioequivalence Studies of Medicinal Product:

test and reference products;

subjects of studies;

study conduct;

statistical evaluation of primary endpoints;

parent compound or metabolites;

enantiomers;

endogenous substances;

medicinal products with narrow therapeutic index (in addition narrowing of the acceptance criteria of C_τ might be necessary);

highly variable active substances and medicinal products;

linearity.

ADDENDUM 1
to Annex No. 10
to the Rules for Conducting
Bioequivalence Studies of Medicinal Products
within the Eurasian Economic Union

Sensitization and irritation test for transdermal products

1. This Addendum provides recommendations on the study designs and scoring systems, which may be used to test skin irritation and sensitization during development of transdermal products with a new chemical entity or generic transdermal products. The design may be adapted for the particular situation.

2. The condition of the skin may influence on the absorption of an active substance from a transdermal system and affect its efficiency and (or) safety. Therefore, skin irritation and sensitization should be assessed.

3. To fully evaluate the equivalence of a generic transdermal product to the reference product, the similarity has also to be demonstrated for skin irritation and sensitization unless otherwise rationalized by, for example, very close quantitative and qualitative composition.

4. The strength included in the test is determined by considering the following factors:

retrospective experience of application in humans according to scientific literature;

previously conducted tests of sensitization (irritation) in animal;

safety issues specific to each particular pharmaceutical substance under study.

1. General study design for a generic product

5. The study suggested has an active- and placebo-controlled, multiple-dose, three-phase, parallel-group design.

In case simultaneous application of test product and reference product is impossible since, under off-label use, doubled amount of pharmaceutical substance would be introduced which might have life threatening consequences the use of a lower strength is acceptable for products with proportional size.

Screening evaluations are performed within a 14-day period prior to application of the patches. Screening evaluations should consist of a medical history, complete physical examination, 12-lead electrocardiogram (ECG), laboratory tests (including serum chemistry, haematology, and urin alysis), and urine drug screen.

Subjects are divided into one of two analysis groups (Group 1 and Group 2) and are evaluated for cumulative dermal irritation and contact sensitization. Test transdermal patch, reference and placebo patches should be randomly applied on the back or other test areas of subjects in the two groups, if permitted by the Summary of Product Characteristics. Skin reactions have to be evaluated by a trained observer blinded to the product distribution. In order to avoid overreaction, the test termination criteria should be provided.

Each subject participates in the following three consecutive study phases.

Induction (cumulative) irritation phase

6. Group 1 subjects are applied test, reference, and placebo patches to randomly selected treatment areas for 21 consecutive days. Group 2 subjects

are applied test, reference, and placebo patches to randomly selected treatment areas three times per week over a period of 21 days (a total of nine applications). In Group 2, the patches remain on skin for 48 hours on weekdays and 72 hours – on weekends. The new patch should be applied to the same site as the previous one. If the next patch is to be applied within 1 hour after removal of the previous one, the administration period of the new patch can then be reduced for this time period.

Rest phase

7. Following the induction (cumulative) irritation phase, each subject enters a two-week rest phase. No patches are applied during the rest phase.

Challenge phase

8. Following the rest phase, patches are applied to new skin sites within the designated areas for 48 hours.

9. In addition to dermal assessments at 0.5 and 24 hours after patch removal, subjects participating in the challenge phase also return for examination on days 40 and 41 for additional dermal assessments at 48 and 72 hours after removal of the last patch.

10. To minimize the effect of inter-subject variability, each study participant receives all three compared products simultaneously. In addition, to control for the unlikely possibility of a «product - applied site» interaction, theses three products should be randomly assigned to three application areas so that each product occupied each application area with approximately equal frequency among the panel of study participants.

11. Dermal response has to be assessed for all subjects in Group 1 and Group 2. Application sites for both groups are evaluated for skin irritation 30 minutes after patch removal (score of dermal response and score of other effects scores determined). New patches are applied every 1 hour after removal of the previous one during the induction (cumulative) irritation phase.

12. To evaluate contact sensitization during the challenge phase, test, reference, and placebo patches are applied simultaneously for 48 hours to previously unused sites on Group 1 and Group 2 subjects. Application sites are evaluated at 0.5, 24, 48, and 72 hours after patch removal.

13. Skin reactions are examined and graded using the scoring scale given in Table 1 (dermal response) and Table 2 (other effects).

Table 1

Dermal response scoring scale

Score	Definition
0	No evidence of irritation
1	Minimal erythema, barely visible
2	Definite erythema, readily visible; minimal oedema or minimal papular response
3	Erythema and papules
4	Definite oedema
5	Erythema, oedema and papules
6	Vesicular eruption
7	Severe reaction spreading beyond test site

14. Each application site receives a separate dermal response score and other effects score. The assessment the dermal response scores requires that

at least 25% or more of the patch area demonstrate the response. During the challenge phase (contact sensitization assessment), only combined dermal response scores ≥ 2 are recognized as a positive response.

Table 2

Other effect score

Score	Definition
0	Not observed
1	Slight glazed appearance
2	Marked glazing
3	Glazing with peeling and cracking
4	Glazing with fissures Film of dried serous exudates covering all or part of the patch site Small petechial erosions and (or) scabs

15. «Severe» reaction to the test product are defined as a dermal response score of 3 – 7 or any dermal score combined with other effects rating of 4 or greater.

Table 3

Assessment of dermal response and other effects of the test, reference and placebo products

Group	Phase	Evaluation by observer	Assessment of test, reference and placebo products
Groups 1	Induction phase (cumulative) irritation	Dermal response score Other effects score	Mean irritation score = average score of dermal response Total cumulative irritation = score sum of dermal

Group	Phase	Evaluation by observer	Assessment of test, reference and placebo products
			irritation Combined dermal response = score sum score sum of dermal irritation and other effects score Mean combined dermal response score
Groups 1 + 2	Challenge phase (contact sensitization)	Dermal response score Other effects score	Combined dermal response score 2:2

16. The general analysis compares the mean irritation scores (mean value of dermal response for all cases) and the total cumulative irritation scores (sum of the dermal response scores for all cases) of the test and reference products. A predefined statistical analysis based on a non-inferiority approach is deemed sufficient to obtain a positive assessment of benefit/risk ratio for such a product. The two one-sided t-test method should be used to compare the irritation scores between products. For each parameter, the least mean squares for each product are derived from an analysis-of-variance model where subject and product are fixed effects. The ratio of the least mean squares of the test product to the reference product has to be calculated, along with its 90% confidence interval. If a 90% confidence interval falls completely within the interval of 0.8 to 1.25, it leads to the conclusion that the two products are equivalent.

17. The assessment of contact sensitization is performed during the challenge phase when the dermal response scores equal to or greater than 2. No statistical analysis has to be performed on these data.

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ADDENDUM 2
to Annex No. 10
to the Rules for Conducting
Bioequivalence Studies of Medicinal Products
within the Eurasian Economic Union

In vivo skin adhesion

I. Transdermal drug delivery systems containing a new or known active substance

1. The investigation of *in vivo* adhesive performance is usually part of the efficiency studies. Based on risk analysis and the instructions for the use of specific products, the robustness of the product to normal human behaviors (for example, moisture resistance to washing, showering, saunas, use of moisturizers and risk of removal during exercise and (or) sleeping, possible transfer to partners or family) should be evaluated. Accidental transfer of a patch to the skin of a non-patch wearer has to be prevented as well as other poor-adhesion related risks have to be minimized by ensuring acceptable adhesion characteristics of the patch.

2. The adhesion is defined as the percentage of area that remains adhered at the end of the dosing interval.

3. In general, it is expected that the 90% confidence interval of mean area of adherence of the test product at the end of the dosing interval should be above 90%. Any non-compliance with requirements has to be rationalized considering all potential risks associated with the incomplete attachment of the patch.

II. Transdermal drug delivery system which is an analogue of a marketed transdermal drug delivery system

4. The study of *in vivo* adhesive performance may be included in the study of clinical pharmacokinetics (both single dose and multi dose), or may be an independent study with either patients or volunteers. In general these studies should ensure adequate adhesion properties in the targeted population, which implies that different studies may be required to study adhesion and pharmacokinetics.

5. For transdermal patches presented in several strengths, the largest patch sizes should be tested *in vivo*, unless otherwise rationalized.

1. Conduct of an adhesion study

6. In General, re-fixation of the patch is not allowed, for example, by over-taping. However, in case a product has to be used in accordance to the the Summary of Product Characteristics with a special layer designed to provide sufficient adhesion, the adhesion studies are to be performed using this separate layer.

7. The frequency of assessment should be stated and rationalized, and should include time points of application and removal of transdermal patches. In general, the frequency of assessment should depend on the wearing period of the patch. Satisfactory and unsatisfactory performance might also be recorded by photographs.

8. In those cases where adhesion is investigated in the pharmacokinetic multiple dose study, sample size calculation should consider not only the pharmacokinetic endpoints but also the hypothesis of adequate adhesion.

9. A descriptive summary of the results should be provided. The results should be presented for each product in tabular and graphical formats with explanations.

10. In addition to the table including the individual values of percentage of adhesion in time, with their corresponding descriptive statistics, the table below could be used for descriptive presentation of the study results.

Adherence	Evaluation time point							
	..h		..h		..h		..h	
	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)
Greater than or equal to 90%								
Greater than or equal to 80%								
Greater than or equal to 70%								
Greater than or equal to 60%								
Adherence	Evaluation time point							
	..h		..h		..h		..h	
	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)	Ref. No. (%)	Test No. (%)
Greater than or equal to 50%								
0 to less than 50 %								

11. In addition to the individual and mean percentage of adhesion in time, a histogram of the adhesiveness in the two treatment groups should be presented.

2. Assessment criteria

12. The main purpose of the assessment:

a) adhesion is defined as the percentage of area that remains adhered at the end of the dosing interval.

b) in general, it is expected that the 90% confidence interval of mean area of adherence of the test product at the end of the dosing interval should be above 90%. Thus, this should be the main object of comparison;

c) if it is assumed that this requirement is unlikely to be met, it may be possible to establish non-inferiority of the test product in relation to the reference product. This may be possible if the reference product has poor adherence (less than 90%). The lower limit of the 90% confidence interval for the difference of adhesiveness (test product minus reference product), using the percentage of adhesion as continuous variable, should not be less than 10%.

13. In addition, it is necessary to evaluate and compare:

the percentage of adhesion for all time-points to assess dynamics how adhesion changes during study;

the proportion of subjects maintaining greater than 90% adherence at each evaluation time-point.

the proportion of subjects with a significant degree of detachment (more than half of the patch lifting off the skin or falling off) for each product at all time points;

the number of patches that are completely detached at each evaluation time-point;

the cases of complete detachment should be analyzed, poor adherence cases should be analyzed and possible causes and risk factors should be established.

14. The qualitative evaluation should also include:

the presence of residues when removing the release layer and transdermal patch;

the presence of flow of the adhesive substance from under the patch, which may, for example, lead to the formation of dark ring around the transdermal patch, patch movement or displacement, wrinkling.

The results of the study should be included in the Summary of Product Characteristics.

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ADDENDUM 3
to Annex No. 10
to the Rules for Conducting
Bioequivalence Studies of Medicinal Products
within the Eurasian Economic Union

In vitro in vivo correlation

I. Introduction

1. An *in vitro in vivo* correlation (IVIVC) of data is a mathematical model characterizing the relationship between a property of a dosage form (mainly dissolution or release of active substance) established *in vitro*, and a corresponding *in vivo* response (mainly plasma concentration of active substance or its amount absorbed). It is evident, that such a relationship occurs only if the medicinal product controls the rate of appearance of the active substance in the plasma.

2. When a modified release product is developed, it is highly recommended to establish an IVIVC:

to determine *in vivo* release and effect on absorption due to the related dosage form;

to establish the *in vivo* significance of *in vitro* dissolution tests and related specifications for dissolution;

to rationalize biowaiver requirements in later phases of clinical development or post-authorization if there are changes in formulation.

3. There are several levels of IVIVC: A, B and C. Level A of IVIVC, in contrast to levels B and C, predict the entire «concentration – time» profile

and in this regard, it is strongly recommended to achieve it. Where an IVIVC is used to support a biowaiver, a level A correlation is, as a rule, a prerequisite.

4. The usefulness of an IVIVC depends on how accurately it can predict achieved plasma concentrations from any set of data obtained *in vitro*. This, in turn, is largely dependent on the design of the *in vitro* and *in vivo* studies used to develop and validate the IVIVC.

II. Study design

5. As a rule, two or more products exhibiting the same release mechanism with sufficiently different dissolution profiles and an appropriate reference product (for the purpose of deconvolution) (RFD) with rapid release of active substance (for example, oral solution or immediate release product) are administered in a cross-over study in healthy volunteers. Other designs are also possible (for example, parallel groups, randomized or partially or fully randomized) and should be selected on a case by case basis depending on the properties of the modified release product, variability, tolerability, etc. The IVIVC study for modified release medicinal products is conducted under fasting condition, even when the product is recommended to be taken with food. The active substance content in plasma or blood (parent or other appropriate analyte according to the Rules for Conducting Bioequivalence Studies of Medicinal Products) is defined as a function of time.

6. Extrapolation beyond the range of products used in IVIVC development and validation is not acceptable for regulatory purposes (for example,

specification preparing and biowaiver requests). Thus, the choice of products requires careful consideration, the various aspects of which (release mechanism, the way to ensure sufficient differences between products, etc.) are given in the Guidelines on Quality for Oral Modified Release Drugs. Since the sensitivity of the «concentration – time» profile of any active substance depends on its own pharmacokinetic properties, the selection of products is advisable to base on the expected «plasma concentration – time» profiles (simulation of the use of theoretical IVIVC relationship or range of possible relationships and the known pharmacokinetic properties of the active substance).

7. While it is acceptable to use different dosage strengths to establish an IVIVC or to assess external predictability (see section 3.3), it should be noted that different dosage strengths of the same product are, as a rule, not considered to represent «different» release rates. For this reason, the assessment of «differences» in dissolution profiles of different products is, as a rule, based on a percentage of labelled (or actual) content.

1. Role and choice of reference product for deconvolution

8. A reference product for deconvolution is a fast release formulation included in IVIVC studies to evaluate the *in vivo* release of active substance as a function of time for each modified release product (see section 3.2). The «*in vivo* release – time» profile of oral modified release medicinal products is normally obtained by deconvolution. It truly reflects *in vivo* release of the active substance only if the reference product is an oral solution (and there is no precipitation from this solution in the stomach or gastrointestinal tract). If the rate of dissolution from an immediate release product exceeds its

absorption (which is, as a rule, maintained for active substances selected for the development of a modified release product), immediate release products may be used as a reference product in studies, which will also show a good approximation of the release of the active substance *in vivo* from modified release medicinal products. Sometimes an intravenous product is used as the reference product for IVIVC. It also allows adequate approximation of *in vivo* release of active substance if the absorption is sufficient fast (for example, for products with high permeability). If permeability contributes (in addition to release from the formulation) to the rate of active substance absorption from the modified release medicinal products, an oral solution is the best choice of reference product (it is better than an intravenous product or immediate release product). In respect of active substances with low solubility and (or) permeability, particularly where permeability changes throughout the gastrointestinal tract, the value may represent approaches to IVIVC based on PBPK modelling.

9. An appropriate reference product for intramuscular (subcutaneous) depot formulations is an aqueous solution administered by the same route (preferable) or an intravenous product. An appropriate reference product for transdermal drug delivery systems is an intravenous product.

10. The reference product should be included in every study, the data of which will be used to establish the IVIVC as well as to assess internal or external predictability. The advantage of including a reference product in IVIVC studies is that it increases the probability of successful IVIVC establishment and validation, particularly for external predictability assessment purposes. The reference product is one of the most important design elements of a successful IVIVC because it normalizes differences in the pharmacokinetics of the active substance on an individual basis. It is used

in every method of data analysis for both internal and external validation. It is especially important where inter-subject variability is moderate to high and where subject numbers of a study do not compensate it. If variability is low and (or) subject numbers are high enough, it may be possible to establish and successfully validate an IVIVC without using a reference product (for example, using literature data or a previously established population pharmacokinetic model). However, in order to make an informed decision it is optimal to establish it by simulation, using the known variability and the proposed design of the study. It is possible to use a reference modified release product for generic modified release medicinal products to normalize differences in clearance between subjects, although this is likely to be less reliable. This strategy may also be evaluated by simulation taking into consideration the variability of the reference product and reference modified release product.

2. Sampling time

11. Issues for the selection of time points for *in vitro* sampling are discussed in the Guidelines on Quality for Oral Modified Release Medicinal Products. When selecting temporary sampling points for *in vitro* dissolution studies and *in vivo* blood (plasma) samples, it is necessary to take into account that the data in the IVIVC analysis will be combined. Thus, an integrated approach to the design of the IVIVC study (including *in vitro* dissolution testing) is encouraged.

12. The selection of time points for sampling of blood (plasma) is best made based on simulations using the actual (or modelled) *in vitro* release data for the clinical batches manufactured for the IVIVC study. If the *in vitro*

dissolution is affected by pH or dependent on rotation speed, dips per minute (dpm) or flow rate (depending on the apparatus), it is advisable to do simulations using the range of *in vitro* dissolution profiles in order to design a sampling regimen to cover the range of potential *in vivo* behaviors. In addition, if there is some a priori understanding of the probable IVIVC relationship this is best built into the initial simulation. For example, for injectable controlled release products, the *in vitro* dissolution test is often carried out within 24 to 48 hours, whereas the estimated duration of *in vivo* delivery is 1 to 2 months. Thus, a time-scaling factor (or to account for uncertainty in expected *in vivo* release, a range of factors) may be anticipated in advance and built into the model to provide a more realistic picture of the expected *in vivo* behavior and better choice for appropriate time points of sampling for the test products.

3. Number of subjects

13. The number of subjects to be included in an IVIVC study is dependent the variability between individuals and intraindividual variability of absorption, and pharmacokinetics of the active substance of the product. Although no clear recommendations can be given, a pragmatic approach is to include at least 12 subjects in a cross-over IVIVC study.

III. IVIVC determination and validation

1. General provisions

14. The ultimate goal of IVIVC determination is to be able to reliably predict the entire dynamics of plasma concentration change in time from a modified release product based on *in vitro* release data. In principle, any

methodology that is scientifically based is acceptable to be used for this. Although some approaches are described below, methodology continues to evolve so the list of methodologies used should not be considered as exhaustive. Since the purpose of the IVIVC determination is to be able to predict using various *in vitro* release data without obtaining data on the plasma concentration *in vivo*, achieved after the application of the modified release product, it is a prerequisite that a single IVIVC relationship is applicable to all products used in its determination and validation.

2. Acceptable methods of data analysis

15. Two general categories of mathematical approaches to IVIVC modelling are one- and two-stage methods. The two-stage method is based on deconvolution. One-stage methods include a method based on convolution and a method based on differential equation and use of PBPK models.

16. Methods based on deconvolution include two stages of data analysis and may be used as the primary IVIVC analysis method or for exploratory analysis preceded by a one-stage method(s). The first stage employs deconvolution to estimate the dynamics of *in vivo* absorption. Non-compartmental methods of deconvolution are preferred over compartmental methods such as Wagner-Nelson or Loo-Riegelman. Deconvolution methodology is included in commercially available software for pharmacokinetic analysis. As a rule, it involves fitting of the single impulse response function (Cδ) to the reference product data for each individual subject followed by deconvolution of individual subject data for each modified release product according to the following relationship to derive the *in vivo* input rate, r(t):

$$C(t) = r(t) \times C_\delta = \int_0^t C_\delta(t-\tau) r(\tau) d\tau$$

where:

C – is plasma concentration;

Cδ – is the single impulse response (i.e. the plasma concentration profile resulting from instantaneous absorption of a single dose of active substance);

* – is the convolution operator.

17. The second stage establishes the relationship between cumulative *in vivo* absorption and *in vitro* product release. In accordance with the generally accepted recommendations in mathematical modelling, it is necessary to strive for savings and use a simple model to describe the data. Typically, models with increasing complexity are used, starting with linear relationships and increasing complexity as necessary according to the data and considerations of biological plausibility. A linear relationship between *in vivo* absorption and *in vitro* release, although desirable, is not necessary. In addition, there are many physiological and physical and chemical factors that make this less likely. In principle, if there is the rationale based on an understanding of composition, physical and chemical, pharmacokinetic and physiological factors controlling the release of active substance *in vitro* and *in vivo*, any relationship that is applicable to all IVIVC products is acceptable including sigmoidal, Hill, using the parameters and approaches of time-scaling and time shifts that account for incomplete absorption (for example, the time cut-off of absorption for oral medicinal products). Different time ranges for each medicinal product indicate the absence of a single relationship for IVIVC products. Methods based on deconvolution are particularly helpful for exploratory data analysis during the model building

process, as they provide graphical output (cumulative amount absorbed *in vivo* versus cumulative amount released *in vitro* and Levy plots: absorption time for a specific portion of dose *in vivo* versus absorption time for a specific portion of dose released *in vitro*). This plot may be used to identify appropriate models for the IVIVC relationship and obtain the necessary initial parameter estimates required for one-stage modelling methods.

18. Methods based on convolution-based differential equation and PBPK model are classified as one-stage methods because modelling involves using the obtained data directly without transformation (i.e. without deconvolution). One-stage approaches provide a number of advantages over methods based on deconvolution, as the model predicts directly the «plasma concentration – time» profile; modelling focuses on the ability to predict measured quantities, and not indirectly calculated quantities such as the cumulative absorbed amount. In addition, these results are easier to interpret in terms of the effect of *in vitro* release on conventional bioequivalence parameters. The compartmental approach allows for nonlinear (for example, Michaelis-Menten) pharmacokinetics, whereas the method based on convolution involves only linear kinetics. Despite the fact that the methods based on convolution and differential equation are one-stage, they differ in the form of the relationship between *in vitro* release and plasma concentration of active substance. The convolution-based approach uses the integral transformation shown above with for the relationship between the concentration of the modified release product, C(t), given the *in vivo* input rate, r(t), and single impulse response, Cδ:

$$C(t) = r(t) \times C_\delta = \int_0^t C_\delta(t-\tau) r(\tau) d\tau$$

The approach based on the differential equation uses a traditional compartmental model of pharmacokinetics of the active substance which also includes an input function.

In both cases, an IVIVC equation determines the relationship between release of active substance *in vitro* [$r_{dis}(t)$] and its absorption *in vivo* [r(t)]. The simplest relationship characterizes how the dissolution of the active substance reflects the rate of absorption. In this case

$$r(t) = r_{dis}(t)$$

В уравнение IVIVC можно включить различные, более сложные функции, учитывающие латентные периоды абсорбции, различие в сроках растворения *in vivo* и абсорбции *in vivo*, а также изменение permeability through the gastrointestinal tract may be included into the IVIVC equation. For example, the following equation includes a latent period (t_0), a scaling factor (s_1), and a scaling factor (sr) that allows incomplete absorption or use of different units between *in vitro* dissolution and *in vivo* absorption.

$$r(t) = s_r \cdot r_{diss}(t_0 + s_1 \cdot t)$$

The approach based on the differential equation uses a traditional compartmental model of pharmacokinetics of the active substance which also includes an input function. Alternatively, PBPK model may be used. This model should be mechanistic and have sufficient experimental data to adequately describe the absorption, metabolism, distribution, and elimination phases of the active substance being tested. Similar to the convolution method based on the differential equation, a PBPK approach as an input uses the *in vitro* release profile which gives a plasma profile that predicts the *in vivo* performance of the medicinal product.

$$r(t) = \varphi_{abs}(t) s_r r_{dis}(t_0 + s_1 t)$$

Where a two-stage approach is used, the average absorption profile is obtained after averaging of the individual subject absorption profiles (i.e. based on the results of individual deconvolution), rather than by deconvolution of the average «concentration – time» profiles. Unless the *in vitro* dissolution data are particularly variable, the use of average dissolution normally has little impact on the result of data analysis and is considered as an acceptable practice.

Qualification and assessment of the IVIVC model predictability

19. Model selection should be based on the understanding of the physicochemical properties of the active substance, its absorption characteristics, the dissolution test characteristics and criteria for assessing goodness of fit (for example, check of predictive information based on existing data). The purpose of the model is to be able to predict with adequate accuracy the expected «plasma concentration – time» curve based on the *in vitro* dissolution data of a modified product. This is demonstrated by a graphical comparison of predicted and actual concentrations and calculation of prediction errors for summary parameters including at least C_{max}, AUC_{0-t} and $_{partial}AUC$.

20. Where PBPK models are used for IVIVC development, it will be necessary to demonstrate that the model predicts the reference product data as well as the modified release product data. Sufficient data should be provided to support the performance of the model.

21. Most IVIVC analyses use averaged *in vitro* dissolution to predict an averaged *in vivo* «concentration – time» profile. This approach is not able to

properly account for random variation *in vitro*, but more importantly, *in vivo*. From this point of view, the one stage approaches offer the advantage since they may be used to analyse nonlinear mixed effects, which allows to include individual variability in the model, which potentially improves the reliability of the model in predicting bioequivalence of new medicinal products.

22. In general, an IVIVC model is considered to be sufficiently accurate if the entire «concentration – time» curve can be well predicted based on the visual inspection and the prediction errors are within acceptable limits. Internal predictability is assessed using the IVIVC model of the «concentration – time» profile based on the respective dissolution data for each product. The summary parameters (Cmax, etc) are calculated based on the predicted «concentration – time» curve and compared to the respective summary parameters of the actual data. The absolute value of the prediction error for all summary parameters should not exceed 15% for each product and the average prediction error for all products included in IVIVC development should not exceed 10% for each summary parameter. If an individual product is found to be inadequately predicted by the IVIVC, it is acceptable to redevelop the IVIVC excluding the outlier product, which will result in the inclusion of a narrower range of dissolution data in IVIVC. However, this will then determine the range within which the IVIVC is accepted as predictive, thereby affecting the possibility of the rationale of specifications and biowaivers. At least two products should remain and the exclusion should be supported by analysis of possible reasons for the deviation (for example, due to the release mechanism, production process).

23. In addition to evaluation of internal predictability with the use of the batches included in a formal IVIVC study, it is recommended to continue to demonstrate the applicability of the IVIVC with additional development

batches (for example, large scale batches used in pivotal studies, additional strengths, any later formulation changes that were studied *in vivo*, etc.). Ideally, whenever pharmacokinetic studies of products with different *in vitro* release profiles are conducted, these data should be used to obtain or strengthen the evidence supporting the *in vivo* in the *in vitro* dissolution test. This can be done through a cross-development of IVIVC using small-scale batches and external validation using large scale batches. In any case, any IVIVC development should demonstrate that the relationship is true for batches reflecting the properties of the product being introduced to the market.

24. The procedure for analysis of external predictability coincides with the procedure above using the IVIVC previously developed. The «concentration – time» profiles are predicted based on the pharmacokinetics of the fast release product (i.e. the reference product) included in the study for external validation purposes and the *in vitro* dissolution data for the particular batch used for external validation. The absolute value of the prediction error for all summary parameters should be less than 10% for each product used for external validation.

Reporting

25. The IVIVC report should include a list of all *in vivo* studies conducted with the modified release product and a rationale for the selection of data included in IVIVC analysis. The data list should include: individual data and summary statistical data for *in vitro* dissolution, «plasma concentration – time» data, obtained pharmacokinetic parameters and cumulative amount absorbed (obtained from deconvolution, even if a one stage method is used for model development) for all batches.

26. Graphical displays should include *in vitro* dissolution in time (showing batches of clinical significance, such as the product to be introduced to the market, etc.), cumulative amount absorbed in time, absorption rate in time, comparison of dissolution and absorption time courses (to evaluate different time frames, latent time periods between data *in vitro* and *in vivo*) and cumulative amount absorbed *in vivo* (% relative to reference product) versus amount released (% of dose) at same time *in vitro* (with overlay of 1:1, regression lines as appropriate) for all products included in IVIVC analysis. Where an obvious time difference exists between time courses of *in vitro* release and *in vivo* absorption (i.e. deviating from 1:1), a Levy plot (time for release of a specific percentage *in vivo* versus the time for release of the same percentage *in vitro*) may also be a useful graphical display.

27. The dissolution test method should be described and a rationale of its suitability taking into account the physical and chemical properties of the active substance, etc. should be given.

28. A full description of the modelling methodology and software employed as well as the basis of decisions should be given, supported by a analysis of the formulation, physicochemical, pharmacokinetic and physiological factors controlling release of the active substance *in vitro* and *in vivo*. Where a compartmental deconvolution method is used (for example, Wagner-Nelson or Lou-Riegelman), the suitability of the approach should be analyzed.

29. Plots evaluating goodness of fit, appropriate to the modelling methodology employed, should be presented as well as final parameter estimates for all fitted data (for example, *in vitro* dissolution and *in vivo*

absorption in case a model is used for interpolation, as well for the IVIVC model itself).

30. The table should contain the «plasma concentration – time» data, predicted by the final IVIVC model, the obtained parameters and the associated prediction error. Graphical comparison of predicted and actual «concentration – time» profiles should be provided.

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ADDENDUM 4
to Annex No. 10
to the Rules for Conducting
Bioequivalence Studies of Medicinal Products
within the Eurasian Economic Union

Summary of brief recommendations for conducting study in abridged marketing authorization

Table 1

Prolonged release single unit product (according to the Summary of Product Characteristics, the product should be taken under fasting or and fed conditions)

Strength	Single dose study under fasting conditions **	Single dose study under fed condition **	Multiple dose study under fasting conditions *
high	Yes	Yes	Yes
middle	Yes	biowaiver, if shape is similar ***	biowaiver ***
low	Yes	biowaiver, if shape is similar ***	biowaiver ***

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* see criteria for necessity to conduct study in subsection 2, section VI of the Annex

** bracketing approach possible if criteria (subsection 7, section VI of the Annex) are met

*** if criteria (see section VI of the Annex) are met, biowaiver to some strengths or bracketing approach are possible

Table 2

Prolonged release single unit product
(according to the Summary of Product Characteristics,
the product is taken under fed conditions)

Strength	Single dose study under fasting conditions [**]	Single dose study under fed condition [**]	Multiple dose study under fasting conditions [*]
high	Yes	Yes	Yes
middle	biowaiver, if shape is similar [***]	Yes	biowaiver [***]
low	biowaiver, if shape is similar [***]	Yes	biowaiver [***]

[*] see criteria for necessity to conduct study in subsection 2, section VI of the Guidelines

[**] bracketing approach possible if criteria (subsection 7, section VI of the Guidelines) are met

[***] biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 3

Prolonged release multiple unit product (according to the Summary of Product Characteristics, the product should be taken under fasting or and fed conditions)

Strength	Single dose study under fasting conditions	Single dose study under fed condition	Multiple dose study under fasting conditions [*]
high	Yes	Yes	Yes
middle	biowaiver [**]	biowaiver [**]	biowaiver [**]
low	biowaiver [**]	biowaiver [**]	biowaiver [**]

[*] see criteria for necessity to conduct study in subsection 2, section VI of the Guidelines

[**] biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 4

Prolonged release multiple unit product
(according to the Summary of Product Characteristics,
the product is taken under fed conditions)

Strength	Single dose study under fasting conditions	Single dose study under fed condition	Multiple dose study under fasting conditions*
high	Yes	Yes	Yes
middle	biowaiver**	biowaiver**	biowaiver**
low	biowaiver**	biowaiver**	biowaiver**

* see criteria for necessity to conduct study in subsection 2, section VI of the Guidelines;
** biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 5

Delayed release single unit product (according to the Summary of Product Characteristics, the product should be taken under fasting or and fed conditions)

Strength	Single dose study under fasting condition*	Single dose study under fed condition*
high	Yes	Yes
middle	Yes	biowaiver, if shape is similar**
low	Yes	biowaiver, if shape is similar**

* bracketing approach is possible if criteria (see subsection 7, section VI of the Guidelines) are met;
** biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 6

Delayed release single unit product (according to the Summary of Product Characteristics, the product should be taken under fed conditions)

Strength	Single dose study under fasting condition**	Single dose study under fed condition**
high	Yes	Yes
middle	biowaiver, if shape is similar**	Yes
low	biowaiver, if shape is similar**	Yes

* bracketing approach is possible if criteria (see subsection 7, section VI of the Guidelines) are met;

** biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 7

Delayed release multiple unit product (according to the Summary of Product Characteristics, the product should be taken under fasting or and fed conditions)

Strength	Single dose study under fasting condition	Single dose study under fed condition
high	Yes	Yes
middle	biowaiver*	biowaiver*
low	biowaiver*	biowaiver*

* biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.

Table 8

Delayed release multiple unit product
(according to the Summary of Product Characteristics, the product is taken under fed conditions)

Strength	Single dose study under fasting condition	Single dose study under fed condition
high	Yes	Yes
middle	biowaiver*	biowaiver*
low	biowaiver*	biowaiver*

* biowaiver to some strengths or bracketing approach are possible if criteria (see section VI of the Guidelines) are met.