

**THE EURASIAN ECONOMIC COMMISSION
BOARD**

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No. 2

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**On Guideline on quality
for oral modified-release drugs**

The Board of the Eurasian Economic Commission, in accordance with Article 30 of the Treaty on the Eurasian Economic Union dated May 29, 2014, paragraph 3 of Article 3 of the Agreement on Common Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union dated December 23, 2014,

in order to eliminate differences in requirements to quality confirmation when changes are made to the registration dossier and to evaluation of equivalence of oral modified-release drugs established by the laws of the Member States of the Eurasian Economic Union,

recommends that the Member States of the Eurasian Economic Union, upon expiration of 6 months from the date of publication of this Recommendation on the official website of the Eurasian Economic Union, apply the Guideline on Quality for oral modified-release drugs according to the Annex hereto, when planning research of bioequivalence in accordance with the Rules of carrying out researches of bioequivalence of medicines within the Eurasian Economic Union approved by Resolution No. 85 of the Council of the Eurasian Economic Commission dated November 3, 2016, and when introducing amendments to the registration dossiers of pharmaceutical

compositions with modified release for oral administration in accordance with the Rules of registration and examination of medical drugs, approved by Resolution No. 78 of the Council of the Eurasian Economic Commission dated November 3, 2016.

Deputy chairman of the Eurasian Economic
Commission Board

K. Minasyan

ANNEX
to the Recommendation of the
Board
of the Eurasian Economic
Commission
dated January 16, 2018 No. 2

GUIDELINE
on quality for oral modified-release drugs

I. General provisions

1. This Guideline defines the requirements to the quality of oral modified-release drugs.

2. This Guideline applies to dosage forms with active substance (substances) release rate and location modified using a specific method as compared to dosage forms with standard release. Such modification may be carried out to prolong the therapeutic activity of the drug, reduce its toxic effect, protect the active substance from degradation due to a low pH value, release the active substance from the dosage form in a predetermined segment of the gastrointestinal tract in order to produce an effect locally or at specific time points, as well as for other purposes.

3. This Guideline covers various parts of the registration dossier, associated with the quality of the drug, and should be considered together with the relevant acts included in the statutory power of the Eurasian Economic Union (hereinafter the Union), as related to clinical aspects of research.

4. This Guideline is recommended for use when applying for registration of a drug to a competent authority of a Member State of the Union (hereinafter referred to as Member State) during examination of registration dossiers, as well as in drug development. This Guideline is used in planning

and conducting research on pharmaceutical development, as well as in drafting registration dossiers.

5. The implementation of this Guideline does not entail new requirements to registered drugs.

II. Definitions

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

«biobatch» is a batch used in a clinical bioavailability (bioequivalence) study or a clinical efficacy study (confirming the existence of functional specifications of the dosage form). The size of a biobatch corresponds to a minimum size of an experimental-industrial batch, i.e. for solid oral dosage forms it amounts to at least 10% of the size of the batch in case of a full-scale production, or 100,000 units of the dosage form (depending on which is greater);

«external predictability» is predictive ability, in respect of which assessment is carried out using the results other than those based on which the «*in vivo*-*in vitro*» correlation was established (it determines how accurately the model predicts the results);

«internal predictability» is predictive ability, in respect of which assessment is being carried out using the results of the initial tests based on which the «*in vivo* – *in vitro*» correlation was established (it determines how accurately the model describes the results used to establish the «*in vivo* – *in vitro*» correlation);

«release controlling excipient» is an auxiliary substance with a determining influence on the release of the active substance;

«zero order release» is the release of the active substance, the rate of which does not depend on time;

«deconvolution» is determination of the kinetics of active substance entering the body (usually by absorption or dissolution *in vivo*) using a mathematical model based on the convolution integral (convolution of functions). For example, the dependence of the absorption rate (r_{abs}) on time which results in the concentration of the active substance in plasma ($c(t)$) can be calculated by solving the following convolution integral for r_{abs} :

$$c(t) = \int_0^t c\delta(t-u) r_{abs}(u) du,$$

where:

$c\delta$ is the function reflecting time-dependence of the active substance concentration obtained in an instant absorption of a single dose of the active substance and is usually calculated based on the results of intravenous jet (bolus) dosing, taking a solution, a suspension, or quickly releasing oral dosage forms with immediate release;

t is time;

r_{abs} is the absorption rate;

u is the integration variable;

«dose dumping» is an unintentionally rapid release of the active substance from the dosage form;

«convolution» is prediction of the active substance concentration in plasma using a mathematical model based on the convolution integral (convolution of functions). For example, to predict concentration of the active substance in plasma ($c(t)$) based on the dependence of the absorption rate (r_{abs}) on time, the following convolution integral can be used:

$$c(t) = \int_0^t c\delta(t-u) r_{abs}(u) du,$$

where:

$c\delta$ is the function reflecting time-dependence of the active substance concentration obtained in an instant absorption of a single dose of the active

substance and is usually calculated based on the results of intravenous jet (bolus) dosing;

t is time;

r_{abs} is the absorption rate;

u is the integration variable;

«*in vivo* – *in vitro* correlation» is linear probabilistic dependence (interrelation) of drug bioavailability parameters on its physicochemical properties or characteristics. The predictive mathematical model describing correlation between the *in vitro* property of a dosage form with prolonged release (usually the rate or degree of dissolution or release of the active substance) and the appropriate *in vivo* response, for example, plasma concentration of the active substance or its absorbed amount;

«modified release dosage forms» are dosage forms with the active substance(s) release rate and (or) location differing from conventional release dosage forms using the same route of administration. Modification is achieved through development of a special formulation and (or) special production technology. Modified release dosage forms include dosage forms with prolonged, delayed (suspended), pulsing and accelerated release;

«prolonged release dosage forms» are modified release dosage forms characterized by a slower release compared to conventional release dosage forms using the same route of administration. Prolonged release is achieved through development of a special formulation and (or) special production technology;

«conventional release dosage form» is a dosage form with the active substance release not modified intentionally using a special formulation and (or) a special production technology. The dissolution profile of the active substance of solid dosage forms significantly depends on the inherent properties of the substance;

«percent prediction error» is the error of prediction of the concentration of the active substance, expressed as a percentage, and calculated using the following formula:

$$PE (\%) = \frac{\text{the observed value} - \text{the expected value}}{\text{the observed value}} \times 100;$$

«side batch» is a batch corresponding to the supposed upper or lower release specification limit *in vitro*, which is compiled based on the described production process by setting its parameters in the range of maximum variability expected as the result of the process validation studies;

«mean absorption time» is the time required for the active substance to reach the systemic circulation after the moment when the drug was used, equal to the mean time of release and *in vivo* absorption processes due to their behavior in the incoming compartment (chamber):

$$MAT = MRT_{oral} - MRT_{i.v.},$$

where:

MRT_{oral} is the mean active substance retention time upon ingestion;

$MRT_{i.v.}$ is the mean active substance retention time upon intravenous administration;

«mean *in vitro* dissolution time» is the mean time of drug dissolution *in vitro*:

$$MDT_{vitro} = \frac{\int_0^{\infty} (M^{\infty} - M(t)) dt}{M^{\infty}},$$

where:

MDT_{vitro} is the average time of drug dissolution in a standardized test solution;

$M(t)$ is the amount of the active substance of a drug which goes into the solution by a specific time point t ;

M^∞ is the amount of the active substance of a drug going into the solution subject to extrapolating observation time to infinity;

«mean *in vivo* dissolution time» is the average dissolution time of a drug *in vivo*, which is calculated by the following formula:

$$MDT_{\text{solid}} = MRT_{\text{solid}} - MRT_{\text{solution}},$$

where:

MRT_{solid} is the mean active substance retention time upon administration of a solid dosage form;

MRT_{solution} is the mean active substance retention time upon administration of a solution;

«mean *in vivo* residence time» is the mean active substance retention time in the body, which is calculated by the following formula:

$$MRT = \frac{AUMC}{AUC},$$

where:

AUC (area under the curve) is the total area under the «concentration-time» pharmacokinetic curve;

$AUMC$ (area under the moment curve) is the total area under the first moment curve of «product of work time by concentration - time»;

«statistical moments» are parameters describing time dependence characteristics of the active substance concentration in plasma (area, mean retention time and mean retention time variance) and the rate of its excretion with the urine;

«sink conditions» are the conditions under which the amount of the substance in the solution upon dissolution test completion does not exceed 30% of its concentration in a saturated solution.

III. Scope of application

7. This Guideline sets out quality requirements to oral modified release dosage forms, in particular the requirements to pharmaceutical development and *in vitro* testing. This Guideline covers only prolonged release and delayed (suspended) release oral dosage forms using the principle of gastro-resistance (resistance to the effect of the gastric juice). Pulsating and accelerated release dosage forms do not fall within the scope of this Guideline. Dosage forms with delayed (suspended) release, developed based on other principles, including release in a certain area of the gastrointestinal tract, influenced by a specific trigger factor (e.g., enzymes) or at a certain time after intake, are not addressed individually.

8. The provisions of this Guideline with respect to prolonged release oral dosage forms are propagated to other modified release dosage forms intended for ingestion or other route of administration.

IV. Prolonged release oral dosage forms

1. Pharmaceutical development

Main Provisions

9. The quality of prolonged release oral dosage forms is continuously improved in the process of developing a new drug. The formulation of the drug is determined when developing with small scale series taking into account the physicochemical properties of the active substance, its stability and absorption characteristics in the gastrointestinal tract. After selecting the components of the drug, a consistent production process scaling starts. Within the specified time, it is suggested that corrective actions are taken necessary for the implementation of a full-scale production. Such corrective actions may be

limited to changing the formulation, manufacturing processes, equipment or production site.

10. In some cases, corrective actions may affect the properties of the drug. In this regard, *in vitro* dissolution test must be developed, able to detect changes that may affect the drug efficacy or safety.

11. Pharmaceutical development must establish connection (qualitative or quantitative) between pharmacokinetic parameters during the release of the active substance *in vivo* and dissolution rate *in vitro*.

12. The formulation of the dosage form established during the development must be assessed under various dissolution conditions to determine its sensitivity (stability) under the expected ambient physiological conditions after administration. The discriminatory power of the conditions for testing selected for routine monitoring can be determined by comparing *in vitro* dissolution data and bioavailability data from various formulations. It is recommended to establish an *in vivo* – *in vitro* correlation. If there is a level A *in vivo* – *in vitro* correlation, dissolution test after appropriate validation can be used as a qualifying control method with relevancy *in vivo*, whereas in the absence of a level A *in vivo* – *in vitro* correlation the test may only be used as a quality control method.

13. If the scaling factor exceeds 10 (compared to lab (experimental) biobatch), in order to verify the conditions selected for dissolution in part of suitability for release of clinical material, scaling and production, upon completion of production scaling it is necessary to compare laboratory (pilot) batches with full-scale industrial batches in a bioavailability study.

Therapeutic goals
and the functioning principle of the release system

14. You must specify therapeutic goals and rationale behind the creation of a prolonged release dosage form. You must specify pharmacokinetic parameters significant for drug development (area under the «plasma concentration-time» curve after receiving the medication (AUC), maximum plasma concentration (C_{\max}), time required to achieve maximum plasma concentration (T_{\max}), plasma elimination half-life ($t_{1/2}$)) and physicochemical characteristics of the pharmaceutical substance (solubility at various pH values, distribution coefficient, particle size, polymorphism).

15. You must provide detailed information on the excipient (excipients) controlling the release, as well as links to regulatory documents on pharmaceutical development.

16. You must describe the following characteristics of the prolonged release system:

- a) method of achieving prolonged release (membrane type, matrix, etc.);
- b) release mechanism and kinetics (diffusion, erosion, osmosis, etc., or combinations thereof);
- c) system type (for example, indecomposable solid dosage form unit, decomposable pill (capsule) containing granules (pellets), etc.).

17. You must confirm that the prolonged release drug retains the characteristics of active substance prolonged release regardless of the variability of physiological conditions. Such variations depend, for example, on the time of transit through the stomach and the intestines, the impact of food, the composition of gastric and intestinal juice under pathological conditions and concurrent alcohol consumption.

18. Oral prolonged release dosage forms should not have scorelines (unless it is justified by special studies), as splitting a modified release dosage

form or otherwise tampering with modified release drugs could adversely affect the characteristics of the modified release dosage form which may lead to dose dumping. Any recommendations for splitting a modified release dosage form must be accompanied by a scientific substantiation confirming absence of influence of splitting on the modified release characteristics, including the results of *in vitro* and/or *in vivo* studies.

Development of *in vitro* dissolution test methods

19. The release rate must be determined *in vitro* using a dissolution test method. A suitable test method must be developed based on *in vitro* physicochemical characteristics and *in vivo* characteristics of the active substance and the drug, taking into account the release mechanism.

20. An *in vitro* dissolution test must:

establish the differences between the batches depending on the critical process parameters (CPP) which may affect the required bioavailability;

determine the consistency of the drug dosage form characteristics from one batch to another (batches for pivotal clinical trials, bioavailability study batches and production batches);

determine the stability of the relevant characteristics of the drug release during the storage life specified by the manufacturer (expiration date) under the specified storage conditions.

In this regard, a prolonged release dosage form should be assessed *in vitro* under various conditions (dissolution media, pH (typically in the range of 1.0-7.5 pH, up to pH 8.0 when required), types of devices, mixing, etc.). You must determine test conditions, including time points and sampling frequency, ensuring the greatest discriminatory power of the test.

21. To ensure adequate control of pH during the dissolution test, buffer solution of suitable capacity should be used. Otherwise, you may need to

monitor pH medium throughout the test. If a surfactant is added into the dissolution medium, its choice and amount must be justified. It is necessary to ensure consistency of the surfactant quality between batches.

22. Adding enzymes in the dissolution medium appears acceptable, and even desirable in cases justified by the drug manufacturer (for example, when you need to deliver the drug into the colon by means of gelatin capsules). When you add enzymes in the dissolution medium, their type and concentration must be justified. In addition, the consistency of the quality of enzymes from one batch to another must be ensured, including activity (IU/mg or IU/ml) or concentration (mg/ml), respectively. The enzyme concentration in artificial gastric juice (simulated stomach acid), artificial intestinal juice (simulated intestinal juice) specified in the Pharmacopoeia of the Eurasian Economic Union (hereinafter referred to as the Pharmacopoeia of the Union) is significantly greater than the corresponding physiological values. Justified enzyme concentrations must be used, if they are an integral part of the dissolution control mechanism. Using a biorelevant medium may improve correlation with the *in vivo* data and identify the potential impact of food.

23. The volume of the dissolution medium must preferably ensure sufficient dilution conditions.

24. For dosage forms with zero-order release kinetics (with or without latent period), it is recommended to set the dissolution rate specification (represented as the percentage of the declared amount of the active substance in the dosage form passing into the solution in one (1) hour («percentage per hour») for a specified period of time). In order to justify that a dosage form may be treated as a form with zero-order release kinetics, graphic dependence of the dissolution rate on dissolution time must be additionally provided. For more detailed information on selection of the device, test conditions,

validation (qualification) and eligibility criteria see the Pharmacopoeia of the Union.

25. Particular attention must be paid to the importance of any changes to the properties of the pharmaceutical substance (e.g., particle size, polymorphism), excipients controlling the release (e.g., particle size, gelling properties), and the production process in terms of their effect on the *in vivo* bioavailability.

26. The method for quantitative determination of the active substance in the dissolution samples must be validated in accordance with the acts included in the statutory power of the Union, taking into account the stability of the active substance dissolved in the medium, and the impact of the excipients.

27. For different dosages of the same drug, identical or, at least, comparable test conditions must be used.

28. In the process of development, the results of *in vitro* dissolution tests for each dosage form unit, their mean value and variability measure (e.g. standard deviation or 95 percent confidence interval) must be submitted for each time point. The use of other statistical approaches must be justified. *In vitro* dissolution profile must be determined for all dosages and any changes in the formulation and/or the manufacturing process of the drug during its development.

The discriminatory power of the *in vitro* dissolution test

29. It must be proved that the *in vitro* dissolution test is able to discriminate drug batches with acceptable and unacceptable release properties under the selected conditions.

30. The discriminatory power of *in vitro* dissolution tests may be confirmed using one of the following methods, listed in order of their priority selection:

a) including batches of a drug not demonstrating acceptable pharmacokinetic parameters *in vivo* in the *in vitro* dissolution test. According to the results of the tests, specifications may be drawn up for rejection of such batches based on dissolution data, which can be substantiated quantitatively using a validated *in vivo* – *in vitro* correlation developed taking into account the batches with unacceptable pharmacokinetic parameters;

b) in the absence of a drug batch with an unacceptable behavior profile *in vivo* – by comparing the dissolution data to the average values of the pharmacokinetic parameter (point estimation) in the *in vivo* studies of pharmacokinetics through checking the rank order of the results;

c) when the provisions of subparagraphs a) and b) of this paragraph cannot be implemented – by a goal-oriented modification of the characteristics of the pharmaceutical substance (for example, by changing the particle size distribution parameter), formulation, and/or production process parameters to get different dissolution profiles *in vitro* without obtaining data of *in vivo* tests for the same batches. Please note that this method can lead to undue discrimination, i.e. even batches with an acceptable *in vivo* behavior profile may be rejected with this quality control method.

Bioavailability Study

31. You must provide a brief description of the bioavailability studies, including information on:

a) pharmacokinetics and, if appropriate, other relevant pharmacokinetic parameters (balanced C_{\min} , partial AUC, C_{\max}/C_{\min} relation, etc.),

b) point estimation and 90% confidence intervals of pharmacokinetic parameters for reproduced drugs;

c) production sites and dates of manufacture;

d) batch numbers and sizes;

e) formulations and dissolution results for the batches used.

32. Bioavailability studies must be conducted with drug batches consisting of 100,000 units or at least 10% of the size of a full-scale production batch, depending on which of these indicators is greater, provided that no pivotal clinical studies were performed with batches of this size. For this purpose, it is sufficient to conduct bioavailability studies using smaller drug batches, if these batches were manufactured in a manner consistent with a full-scale production process. For example, if phase II clinical studies (including pharmacokinetic studies and bioavailability studies) are conducted on the 15 kg batch, provided that pivotal clinical trials have already been conducted on a batch 60 kilograms (when, at the same time, bioavailability studies of this batch are not available), and it is expected that there will be a full-scale production of the 600 kg batch, then no further bioavailability studies for the 60 kg batch are required.

Comparison of dissolution profiles

33. In some cases, to establish similarity, dissolution profiles should be mapped, for example:

after scaling, changing the formulation and/or production process;

in case of extrapolating *in vivo* results when registering various dosages.

Similarity of dissolution profiles should be established using at least 12 individual values for the time point. You should consider the time points and sampling frequency, taking into account *in vitro* and *in vivo* physicochemical characteristics of the active substance and the mechanism of drug release.

34. In case of extrapolating *in vivo* results when registering various dosages of the drug (in the absence of *in vivo* comparative data on all dosages of the investigational drug with a comparator), dissolution of other dosages of

the investigational drug should be compared with the dosage of the tested drug which was used in the bioequivalence study.

35. Dissolution profiles should be compared. At the same time, establishing their similarity may also require confirmation by statistical methods using model-independent or model-dependent criteria, such as:

- a) estimating linear regression of the percentage (amount as a percentage) of the active substance dissolved at certain time points;
- b) statistical comparison of Weibull function parameters;
- c) calculation of the similarity coefficient;
- d) other model-independent or model-dependent criteria (with justification).

Establishing *in vivo* – *in vitro* correlation

36. *In vitro* dissolution test is important in order to ensure the necessary consistency of quality from one batch to another and is a consistency indicator within a batch (when all dosage form units have the desired functional specifications *in vivo*). By establishing a clear correlation between *in vitro* release properties and *in vivo* bioavailability parameters, *in vitro* dissolution test can serve as a surrogate marker of *in vivo* behavior, as well as a consistency measure of therapeutic properties of routinely produced drug batches. When establishing a correlation, variability of data must be recorded and analyzed. Generally, the higher variability of the data used to develop *in vivo* – *in vitro* correlation, the lower confidence in estimating model parameters, and the higher uncertainty in its forecasting *in vivo* behavior.

37. The established level A *in vivo* – *in vitro* correlation reduces the number of *in vivo* studies during the drug development process, is used in compiling specifications and promotes the adoption of certain regulatory decisions (e.g. scaling and making post-registration changes). In this regard,

the applicant should consider the possibility of developing such an *in vivo* – *in vitro* correlation. Furthermore, establishing a level A *in vivo* – *in vitro* correlation allows you to confidently use dissolution tests as a tool for modification management. As an alternative to comparing *in vitro* and *in vivo* data it is permitted to use a mechanistic model (for example, physiology-based pharmacokinetic models (PBPK)).

38. Level A *in vivo* – *in vitro* correlation validation consists in confirming the adequacy of its predictive ability. Level A *in vivo* – *in vitro* correlation is established, for example, based on the deconvolution method, using which *in vivo* absorption or *in vivo* dissolution can be predicted based on *in vitro* studies (Instructions on determining the type of correlation are given in the annex to this Guideline). Validated level A *in vivo* – *in vitro* correlation allows for using the associated *in vitro* dissolution test as a surrogate marker for *in vivo* studies, because the resulting «*in vivo* concentration – time» dependence profile can be predicted using the results of the *in vitro* dissolution test and *in vivo* – *in vitro* correlation equation. This approach assumes the following:

such an *in vivo* – *in vitro* correlation of level C may be used reliably only for interpolation;

the same *in vivo* – *in vitro* correlation model should be applied to all dosage form formulations used in the development and validation of the model;

in vivo – *in vitro* correlation cannot justify recognition of bioequivalence of drugs from different applicants solely on the basis of *in vitro* data.

39. *In vitro* correlation model should be used in order to interpolate within the range of data used for its development, rather than extrapolate outside its operating range. This research principle is especially important when applying to regulatory bodies (for example, dissolution specification

justification and in case of a biowaiver), which is crucial when choosing dosage form formulations included in the *in vivo* – *in vitro* correlation study.

40. To develop and validate *in vivo* – *in vitro* correlation, it is normally recommended to use formulations with widely varying *in vitro* dissolution profiles, since the use of formulations with slight differences in their *in vitro* dissolution profiles will limit the possibilities for extending the range of specifications and the range within which a biowaiver can be justified. It should be kept in mind that in case of extreme versions of formulations various release mechanisms and other biopharmaceutical factors may influence the dependence of the active substance release *in vitro* and *in vivo*, thus hindering obtainment of a single *in vivo* – *in vitro* correlation equation that would describe the behavior of all formulations within the range proposed for the biowaiver. Accordingly, formulations must be selected in such a way that the same mechanism (if possible) would control the release of the active substance both *in vitro* and *in vivo*. This usually limits the range of *in vitro* dissolution profiles used in practice to develop and validate *in vivo* – *in vitro* correlation.

41. When an extreme formulation is subsequently selected for further development of *in vivo* – *in vitro* correlation (i.e. a formulation with the fastest or slowest dissolution *in vitro* among those used in the *in vivo* – *in vitro* correlation), it is appropriate to extend the *in vivo* – *in vitro* correlation validation range by obtaining *in vivo* data for another formulation (with faster or slower dissolution depending on the circumstances) and using this data for external validation of the existing *in vivo* – *in vitro* correlation or re-development and validation of a new *in vivo* – *in vitro* correlation. Thus, it is important for the planned target formulation to be appropriately surrounded by extreme versions.

2. Drawing up specifications

42. Specification is drawn up using discriminatory dissolution tests.

43. Usually, at least 3 points are included in the *in vitro* dissolution specification for a prolonged release oral drug:

a) early time point to exclude dose dumping and/or establish load (initial) dose characterization (usually from 20% to 30% of the dissolved substance);

b) at least one point to ensure compliance with the dissolution profile shape (about 50% of the dissolved substance);

c) one point to secure release of the greater part of the active substance ($Q = 80\%$). If the maximum amount of the dissolved substance is less than 80%, the last time point should be the time when the dissolution profile achieves its plateau.

44. For drugs with zero order release, dissolution rate (time) specification for a given time interval may be more suitable than the total amount of the dissolved substance at a single time point. If the zero order release kinetics is combined with a varying lag-period (effect delay time), this specification is mandatory. The technique for establishing a lag-period is determined by the applicant.

45. A variation allowable around each time point (upper and lower limits) can be established in various ways:

a) in the absence of *in vivo* – *in vitro* correlation. Allowable limits can be obtained on the basis of variation in the *in vitro* dissolution data for series with confirmed acceptable *in vivo* performance (biobatch(es)), or by proving bioequivalence of the batches in the suggested upper and lower limits of the dissolution range (the concept of the «extreme batch»). As a rule, the permissible range of release values at any given time should not exceed the total numerical difference $\pm 10\%$ of the declared active substance content, i.e.

the total variability should amount to 20% (for example, when the declared active substance content is $50\pm 10\%$ it means that the permissible range is from 40% to 60%), if no wider range is confirmed by bioequivalence studies;

b) with an established level A *in vivo* – *in vitro* correlation. Validated level A *in vivo* – *in vitro* correlation allows for using the *in vitro* dissolution data (proposed data, not obtained during monitoring) to replace an *in vivo* study of the formulations within the proposed dissolution specification limits. Dissolution profiles are obtained from the proposed limits using an established *in vivo* – *in vitro* correlation, preferably including the corresponding mathematical description of the *in vitro* dissolution function performance (Weibull function, Hill's equation and so on, based on the behavior of the formulations studied when developing a drug), or, less preferably, based on releases at various time points. The complete profile of the plasma concentration-time dependence is calculated for the proposed upper and lower dissolution limits, as well as on the basis of the obtained *in vitro* dissolution data for the formulation intended for registration (comparator formulation), using a validated *in vivo* – *in vitro* correlation. The corresponding C_{\max} and selected AUC parameter values are calculated for the proposed lower/upper limits, comparator formulation and the obtained relations (the upper limit to the lower limit, the upper limit to the comparator formulation limit and the lower limit to the comparator formulation limit).

46. The basic principle of drawing up a specification is that all batches with parameters between the lower and upper dissolution specification limits must be bio-equivalent to each other. If bioequivalence is based on *in vivo* data, and the permissible range for the maximum difference based on the results of the comparison amounts to 80.00. 125.00% based on confidence intervals around average C_{\max} values and the selected AUC parameter. Despite the fact that some *in vivo* – *in vitro* correlation analysis techniques allow for

quantifying biological variability and predicting confidence intervals, most techniques only predict average data on concentration-time dependence. Thus, the criteria for establishing the boundaries of accepting bioequivalence predictable based on average values (using the dissolution data instead of *in vivo* data and validated *in vivo* – *in vitro* correlations) should be more rigid, i.e. the difference in the C_{\max} values and the selected AUC parameter for average values of concentration-time dependence during *in vivo* tests, predicted for the upper and lower dissolution specification limits, must be less than 20%. The boundaries based on the difference exceeding 20% between the predicted C_{\max} values and the selected AUC parameter for the upper and lower dissolution specification limits must be justified by the drug manufacturer.

47. AUC of the drugs absorbed throughout the entire gastrointestinal tract is often similar for different formulations with widely ranging dissolution rates, so the specification is drawn up based on the C_{\max} parameter rather than AUC parameter. The advantage of using *in vivo* – *in vitro* correlation for drawing up a specification in this case is that at certain time points the boundaries of cumulative dissolution may go beyond $\pm 10\%$, as the effect of different time points on the C_{\max} parameter is not the same. The sensitivity of the C_{\max} parameter to changes in dissolution depends on the pharmacokinetic properties (the shorter the half-life, the greater sensitivity to changes in dissolution) and the *in vivo* – *in vitro* correlation dependence shape (depending on which is faster: *in vitro* or *in vivo* dissolution of the drug).

3. Quality control strategy

48. General requirements for the development and justification of drug quality control strategy are provided in the relevant acts of the Union bodies. Critical quality parameters vital for medicinal product release must be monitored.

49. During pharmaceutical development it is necessary to establish the connection (qualitative or quantitative) of the pharmacokinetic parameters through *in vivo* release of the active substance with the *in vitro* dissolution rate.

50. In the course of an enhanced pharmaceutical development, the compliance of the drug dosage form with the *in vitro* dissolution test requirements can be confirmed by tests during production of the drug in real time. Since the release rate of the active substance may be sensitive to scaling, it is necessary to verify the active substance release predicting technique in full-scale production conditions.

4. Introducing changes in the drug registration dossier

51. The requirements to data justifying the changes to the registration dossier depend on the degree of significance of the change, the presence of a level A *in vivo* – *in vitro* correlation, availability or need to change the dissolution technique (limits). If no bioavailability (bioequivalence) data are presented, it is necessary to justify their absence.

52. If a level A *in vivo* – *in vitro* correlation is established, and the release specification is not changed, the changes can be accepted based on the *in vitro* data, the therapeutic index of the active substance and the predictive ability of the *in vivo* – *in vitro* correlation. In this case, the refusal of the drug manufacturer to conduct bioequivalence studies must be based on the comparison of the predicted profiles of concentration in plasma-time dependence and the related pharmacokinetic parameters for formulations before and after the changes, calculated using *in vitro* data and validated *in vivo* – *in vitro* correlation.

53. With regard to drugs with a proven level B or C correlation, or in the absence of an *in vivo* – *in vitro* correlation, it is necessary to submit

bioavailability (bioequivalence) data, if no justification of the absence of such data is available.

V. Dosage forms with delayed (suspended) release

1. Main Provisions

54. The Pharmacopoeia of the Union defines several dosage forms with delayed (suspended) release: enterosoluble capsules, tablets and granules. This section provides specific instructions for enterosoluble dosage forms. Dosage forms based on other principles are also commonly classified as dosage forms with delayed (suspended) release, including those developed for release in a certain area of the gastrointestinal tract, influenced by a specific trigger factor (e.g., enzymes) or at a certain time after intake. Despite the fact that the principles of pharmaceutical development, drawing up specifications and quality control strategy described in this Guideline may also be applicable to other dosage forms with delayed (suspended) release, it seems appropriate to develop a separate guideline for such dosage forms, based on the principle of matching the appropriate formulation and release mechanism.

55. Many of the provisions stipulated for prolonged release oral dosage forms are also applicable to dosage forms with delayed (suspended) release.

2. Pharmaceutical development

56. The summary of bioequivalence studies, which should be submitted in the registration dossier, includes information on pharmacokinetics and, if acceptable, other parameters (e.g., partial AUC, for reproduced drugs – also a point estimation and 90% confidence intervals), production sites and production dates, batch numbers and sizes, formulations of the dosage forms and dissolution results for the used batches.

57. You should specify the purpose of delayed (suspended) release, for example, protection of gastric mucosa, protection of the active substance from the effects of the stomach acid environment or purposeful release of the active substance in a given segment of the gastrointestinal tract to provide local effect, etc.

58. The release mechanism should be analyzed and the selection of the excipient (excipients) responsible for delayed (suspended) release must be justified, for example, purposeful release at a given pH value, sensitivity to the effect of enzymes, erosion over time, etc.

During pharmaceutical development it is necessary to establish qualitative or quantitative connection between the pharmacokinetic parameters and the *in vitro* dissolution rate which characterizes the release of the active substance *in vivo*.

Depending on the behavior of the drug in the stomach, 2 types of formulations of drugs with delayed (suspended) release can be distinguished:

- single-unit (solid) indecomposable dosage forms;
- decomposable dosage forms containing granules.

59. It is not usually recommended to develop single-unit (solid) indecomposable enterosoluble dosage forms of gastro-resistant drugs, since the period of their presence in the stomach is unpredictable and exceeds that of the decomposable dosage forms containing granules. Therefore, such single-unit (solid) indecomposable enterosoluble dosage forms are at a higher risk of dose dumping and/or have random concentration profiles.

60. When the general characteristic of the drug requires intake together with food or does not exclude it, gastro-resistance tests should be also carried out in conditions specific to the state of satiation. For example, to measure stability upon release in a full stomach, the tests must be carried out at a higher pH value (for example, in a range of 3.0-5.0) using both indecomposable solid

dosage forms and decomposable dosage forms containing granules. A large amount of food in your stomach temporarily leads to an increase in the pH value up to 3.0 or above, that's why a test with pH value of 2.0 will not be sufficiently convincing.

3. Drawing up specifications

61. *In vitro* dissolution test specification of an enterosoluble medicine should include at least 2 time points:

- a) early time point to exclude release in acidic environment (less than 10% of the dissolved substance after 2 hours);
- b) one point to ensure release of the basic amount of the active substance in a neutral or close to neutral environment.

62. Gastro-resistance must be confirmed for 2 hours or longer.

63. Eligibility criteria for the next test stage are specified in the Pharmacopoeia of the Union.

4. Quality control strategy

64. Requirements to the development and justification of the drug quality control strategy can be found in the relevant regulatory acts included in the Union statutory power. It is necessary to monitor critical quality parameters responsible for delayed (suspended) drug release (e.g., integrity of the enterosoluble overpouch).

65. During pharmaceutical development it is necessary to establish qualitative or quantitative connection between the pharmacokinetic parameters and the *in vitro* dissolution rate which characterizes the release of the active substance *in vivo*. In the context of an enhanced pharmaceutical development, the compliance with the dissolution requirements can be confirmed by tests during production of the drug in real time. Since the release

rate of dosage forms with delayed (suspended) release may be sensitive to scaling, it is necessary to verify the project field in the context of full-scale production.

5. Introducing changes in the drug registration dossier

66. Since *in vitro* dissolution testing of gastro-resistant dosage forms with delayed (suspended) release is considered to be relevant for *in vivo* test conditions, changing the excipients responsible for delayed (suspended) release of drugs in a gastro-resistant dosage form is only allowed to be justified on the basis of the *in vitro* test results obtained (when justifications are available). The release profiles obtained from gastro-resistance tests must be consistent.

ANNEX
to Guideline on quality
for oral modified-release drugs

INSTRUCTIONS
on establishing the type of correlation

I. *In vivo – in vitro correlation*

1. To establish the level of *in vivo – in vitro* correlation, various methods are used. There are the following levels of *in vivo – in vitro* correlation:

a) Level A reflects point-by-point relationship between the drug dissolution curve *in vitro* and *in vivo* dissolution curves obtained using the method of plasma concentration data deconvolution (Wagner-Nelson method, Lou Rigelman method, numerical deconvolution) or other relevant methods (methods of modeling based on convolution or differential equations using average data or population pharmacokinetics modeling methods);

b) Level B reflects one-point dependence by one the parameters:

between the mean *in vitro* drug dissolution time and the mean *in vivo* retention time or mean *in vivo* dissolution time using the principles of statistical points analysis;

between the *in vitro* dissolution rate constant (k_d) and the obtained absorption rate constant (k_{abs});

c) Level C reflects one-point dependence between the amount of the substance dissolved *in vitro* in a certain period and an average value of one of the pharmacokinetic parameters (e.g., AUC, C_{max} or T_{max}). If one or more pharmacokinetic parameters correlate with the amount of the dissolved active substance at several dissolution profile time points, it is considered that a multiple level C correlation has been established.

II. Developing *in vivo* – *in vitro* correlation

Level A

2. Recommendations on the research design and subsequent analysis of the *in vivo* – *in vitro* correlation data are contained in the acts included in the statutory power of the Eurasian Economic Union. Typically, 2 or more formulations with sufficiently differing dissolution profiles and a corresponding comparator formulation (for the purpose of deconvolution) with prompt active substance release (e.g., a solution for intravenous administration, a solution for oral intake, or an immediate release dosage form) are applied in the process of crossover studies conducted in healthy volunteers. The concentration of the original (unmodified) active substance in blood or plasma is defined as a function of time. *In vivo* – *in vitro* correlation can be modeled directly according to the active substance concentration in plasma (one-stage approach) or after concentration-time profiles deconvolution for a modified-release formulation in reference to the immediate release formulation (two-stage approach). To ensure that the *in vitro* dissolution test serves as a surrogate marker of *in vivo* behavior and can be used as a tool for monitoring changes, usually a level A *in vivo* – *in vitro* correlation is required.

3. The initial dissolution study of formulations in various tests (conditions) during the drug production makes it possible to determine the test providing the most suitable discriminatory power. Sampling time points in the *in vitro* dissolution test for formulations used in the *in vivo* – *in vitro* correlation study must be sufficiently frequent to completely characterize the dissolution profile, including its plateau (e.g., 3 sequential points differing by at least 5%). A smaller number of sampling time points may be established when conducting a quality control test; however, the reverse isn't true: sampling time points when conducting quality control cannot be applied as

points for *in vitro* dissolution tests to obtain *in vivo* – *in vitro* correlation data, as sparse data may not allow for accurate interpolation between the points, and termination of sampling before reaching the plateau leads to an incomplete release and violates the *in vivo* – *in vitro* correlation validation.

Levels B and C

4. Usually, levels B and C correlation cannot be used by the manufacturer to justify significant changes in the formulation or manufacturing process of the drug. However, multiple level C correlation may serve as an aid in drawing up specification.

5. Multiple level C correlation is developed by establishing a linear correlation based on at least 3 time points between the amount of dissolved substance at 3 or more time points or 3 MDT points, on the one hand, and the corresponding AUC and C_{\max} parameters for some formulations with different *in vitro* dissolution rate profiles, MRT parameter or any other suitable pharmacokinetic parameter (multiple level C correlation), on the other hand. *In vitro* data can be used to predict the *in vivo* functional specifications. Note that if a multiple level C correlation is achievable, it is also possible to develop a level A correlation. Level A *in vivo* – *in vitro* correlation allows you to predict a complete plasma concentration-time profile (providing the necessary information on the profile shape and time required to achieve maximum concentration) in addition to common pharmacokinetic parameters, such as C_{\max} and AUC, while level C multiple correlation only allows you to predict generalized pharmacokinetic parameters. Thus, level A correlation is the preferable approach.

6. The parameters used to establish the *in vivo* – *in vitro* correlation of various levels are shown in the Table.

Parameters used to establish
the *in vivo* – *in vitro* correlation of various levels

Level	Type of dependency	Parameter	
		<i>in vitro</i>	<i>in vivo</i>
A	point-by-point	dissolution profile	pharmacokinetic curve
B	single-point	MDT _{vitro}	MRT, MDT _{vivo}
		k _d	k _{abs}
C	single-point	r _d (T _{20-30%} , T _{50%} , T _{80%})	C _{max} , T _{max} , AUC (mean values)
		Multiple correlation	
		C (T _{20-30%} , T _{50%} , T _{80%}) or C (MDT)	C _{max} , T _{max} , AUC, MRT, etc.

III. Evaluation of the *in vivo* – *in vitro* correlation's predictive ability

7. When using *in vivo* – *in vitro* correlation as a surrogate marker of *in vivo* functional specifications, you should verify that the prediction of *in vivo* functional specifications based on *in vitro* dissolution profile applies to *in vitro* dissolution rates covered by the *in vivo* – *in vitro* correlation. Such an assessment should be reduced to evaluating the prediction of functional specifications or, on the contrary, the prediction errors.

8. When evaluating the predictive ability, it is particularly important to take into account 2 main aspects:

a) the less data is available for the development and assessment of *in vivo* – *in vitro* correlations, the more additional data is required to fully assess the predictive ability of the *in vivo* – *in vitro* correlation;

b) the studied formulations must properly differ in the release rate (for example, by at least 10% of the dissolved amount), which results in a significant difference between the pharmacokinetic parameters considered.

9. The methodology and the predictive ability analysis report are applied in accordance with the manual on pharmacokinetic and clinical study of bioequivalence of modified-release drugs, bioequivalence of liposomal drugs, bioequivalence of corticosteroids for topical use in dermatology, approved by the Eurasian Economic Commission.
