Federal Service on Surveillance in Healthcare and Social Development

Methodological recommendations for drug manufacturers on *in vitro* equivalence test for generic drug products according to biowaiver procedure

(DRAFT)

Moscow 2010

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These recommendations are prepared according to Ministry of Health and Social Development of the Russian Federation Guidance (Guidance on investigation of bioequivalence. Annex 4, 2008); EMEA Guidance (CPMP Note for Guidance on the Investigation of Bioavailability and Bioequivalence. The European Agency for the Evaluation of Medicinal Products CPMP/EWP/QWP/1401/98, 2001); FDA Guidance (Guidance for Industry. Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, 2000); Health Department of Ukraine Guidance (Directive № 190. Order of execution of additional tests on drugs during the expertise of registration documents, 2007); and WHO Guidance (WHO Technical Report Series 937. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Annex 7. Multisource (generic) pharmaceutical products: guidelines on registration requirements to establish interchangeability. Annex 8. Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms, 2006).

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Introduction

At present most of drug products marketed in Russian Federation are generic (multisource) products. For justified conclusion on efficacy and safety of generic drug products approved *in vivo* bioequivalence studies are generally carried out. In addition, it suggested that equivalence of some generic preparation with suitable biopharmaceutical properties may be evaluated under *in vitro* conditions.

One of the modern ways to establish generic drugs interchangeability is *in vitro* dissolution kinetics study, which is performed instead of *in vivo* bioequivalence studies. For this purpose a regulatory drug approval process that includes *in vitro* equivalence test was developed, which is called "biowaiver". Biowaiver procedure is based on API and drug product biopharmaceutical properties: solubility, permeability and dissolution.

Current WHO, FDA, EMA and Health Department of Ukraine allow waiver of *in vivo* bioequivalence studies and exchange them to *in vitro* equivalence test according BCS based biowaiver.

1. Terms

Biowaiver – a regulatory drug approval process when generic drug interchangeability is established based on biopharmaceutical properties an *in vitro* equivalence test instead of *in vivo* bioequivalence studies.

Biopharmaceutical Classification System (BCS) – a scientific framework for classifying active pharmaceutical ingredients based upon their solubility in aqueous solutions with different pH in physiological range and intestinal permeability.

Bioequivalence – two drug products are considered bioequivalent if they provide the same bioavailability of API.

Interchangeable generic (multisource) drug product – an interchangeable pharmaceutical product is one which is therapeutically equivalent to a reference product and can be interchanged with the reference in clinical practice.

Generic (multisource) drug product – a drug product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.

Dissolution kinetics study – test intended for evaluation of dissolution profiles similarity when the quantity of API released is assayed in three or more previously chosen time points.

Immediate release dosage forms – dosage forms which provide 75 % or more API release in 45 min carrying out dissolution test under conditions stated in corresponding compendial monograph or analytical protocol.

Original (innovator) drug product – a drug product which was first authorized for marketing, on the basis of documentation of quality, safety and efficacy.

In vitro equivalence test – a dissolution test that includes comparison of the dissolution profile between the test and reference product (or different doses of the same drug product) in three media: pH 1.2, pH 4.5 and pH 6.8.

Reference preparation (comparator product) – drug product, which is used as a reference when comprising dissolution profiles with test product for *in vitro* equivalence test.

Dissolution profile – a curve, characterizing dependent of API release (%) on time in several (not less than 3) time points.

Therapeutic equivalence – drug products are considered to be therapeutically equivalent if they are pharmaceutically equivalent and after administration in the same molar dose, their effects, with respect to both efficacy and safety, are

essentially the same when administered to patients by the same route under the conditions specified in the labeling.

Dissolution test – test intended for API assay which released in dissolution medium under conditions stated in compendial monograph or analytical protocol at prescribed time point.

Pharmaceutical equivalence – drug products are pharmaceutical equivalents if they contain the same molar amount of the same active pharmaceutical ingredient(s) in the same dosage form.

2. Objects of study

The objects of study are immediate release solid oral dosage forms with systemic action.

3. Reference preparation

The innovator drug product with Marketing Authorization in Russian Federation should be used as a reference preparation.

If the innovator drug product has no Marketing Authorization in Russian Federation, a most widely used generic drug product (market leader) with Marketing Authorization in Russian Federation should be used as a reference preparation.

4. *In vitro* dissolution kinetics studies

This chapter is provided for information only and has no regulatory status.

At present dissolution test is a powerful tool for characterizing the quality of oral pharmaceutical products. Dissolution test is used to developing of new drug products, in choosing among candidate formulations with different composition, to evaluate batch-to-batch consistency, to control changes in technological process, for quality control of finished product.

Dissolution test used as a prognostic tool for oral drug absorption and as an alternative to *in vivo* bioequivalence studies with one prescribed time point may be not enough informative. For this purpose *in vitro* dissolution kinetics study with several time points which involves dissolution profile similarity evaluation gives more reliable data.

NOTE

It should be noted that dissolution test and *in vitro* equivalence test are not interchangeable terms, and their test conditions may be different. Quality control dissolution test is carried out under conditions stated in corresponding compendial monograph or analytical protocol, and in vitro equivalence test conditions are stated in chapter (6.2) of current Guidance.

5. Biopharmaceutics Classification System (BCS)

Biopharmaceutics Classification System was developed by Amidon et al in 1995 and was first mentioned by US FDA in «Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In vitro* Dissolution Testing, and *In vivo* Bioequivalence Documentation». BCS is based on API solubility in aqueous solutions with different pH in physiological range (5.1) and intestinal permeability (5.2):

Class I – "*high*" solubility, "*high*" permeability;

Class II – "*low*" solubility, "*high*" permeability;

Class III – "*high*" solubility, "*low*" permeability;

Class IV – "*low*" solubility, "*low*" permeability.

When *in vitro* equivalence test is carried out, one more biopharmaceutical property of generic drug should be evaluated - dissolution characteristic (5.3). Immediate release dosage forms are also categorized as having "very rapid", "rapid", or "not rapid" dissolution characteristics.

Solubility and permeability are drug substance properties, and dissolution characteristics (“very rapid”, “rapid”, or “not rapid”) are drug product properties.

5.1. Solubility

An API is considered highly soluble when the ratio of highest dose (D, mg) of immediate release solid oral dosage form with Marketing Authorization in Russia to solubility (S, mg/ml) in aqueous media over the pH range of 1,2–6,8 determined at 37 ± 1^{o}C in triplicate is less or equal to 250 (ml).

The volume of 250 ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a 1 glass of water. The highest dose should be soluble in this volume.

5.2. Permeability

When an API is absorbed to an extent of 85% or more it is classified as “*highly”* permeable. Permeability data is considered valid if it is obtained by *in vivo* studies in humans (absolute bioavailability studies, mass-balance studies or intestinal perfusion technique).

Supportive data can be provided by the following additional test methods:

- *in situ* permeability studies (e.g. in rat intestine);
- *in vivo* permeability studies in animals;
- *in vitro* permeability studies (in epithelial cells monolayers, e.g. Caco-2).

NOTE

It should be noted that only *in vivo* permeability data are reliable. Other data should not be taken into account if in *vivo* data are absent.

5.3. Dissolution characteristics

A generic drug product is considered to be very “rapidly dissolving” (equal term: “very rapid dissolution”) when not less than 85 % of the labeled amount of the drug substance dissolves in 15 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media: HCl solution pH 1.2, buffer solution pH 4.5, buffer solution pH 6.8.

A generic drug product is considered to be “rapidly dissolving” (equal term: “rapid dissolution”) when not less than 85 % of the labeled amount of the drug substance dissolves in 30 minutes using a paddle apparatus at 75 rpm or a basket apparatus at 100 rpm in a volume of 900 ml or less in each of the following media: HCl solution pH 1.2, buffer solution pH 4.5, buffer solution pH 6.8.

Other drugs product, which cannot be classified as “rapidly dissolving” or “very rapidly dissolving” are classified as “not rapidly dissolving”.

5.4 Additional API characteristics

This chapter is provided for information only and has no regulatory status.

International Pharmaceutical Federation (FIP) recommends investigating some additional physic-chemical and biopharmaceutical characteristics for biowaiver possibility evaluation:

- polymorphism;
- partition coefficient (*log P*) as indirect permeability indicator;
- acid-base properties (pKa) etc.

6. Biowaiver procedure

For *in vitro* evaluation of generic drugs under biowaiver conditions:

- solubility (5.1) and permeability (5.2) of API;
- dissolution profiles of test and reference preparation in dissolution media pH 1.2, 4.5 and 6.8 (*in vitro* equivalence test);
- dissolution characteristics (5.3) of drug product;
- the excipients used in the formulation;

- possible risks associated with therapeutic index and adverse effects.

Methods

6.1 Solubility and permeability studies

Solubility and permeability of API are evaluated on reliable peer-review literature data. If such data are absent, solubility and permeability of API are determined experimentally.

NOTE

International Pharmaceutical Federation (FIP)[1] (up to December 2009) has prepared 25 review articles – biowaiver monographs on APIs of WHO Model List of Essential Medicines. The monographs have no formal regulatory status, but represent the best scientific opinions currently available; therefore the information presented in biowaiver monographs should be used primary. If biowaiver monograph on evaluated API is not presented, following data sources are recommended:

- M. Lindenberg, S. Kopp, J. Dressman. *Classification of orally administered drugs on the World Health Organization Model list of Essential Medicines according to the biopharmaceutics classification system* / European Journal of Pharmaceutics and Biopharmaceutics, No 58 (2004) 265–278;
- WHO Technical Report Series 937, annex 8 *«Proposal to waive in vivo bioequivalence requirements for WHO Model List of Essential Medicines immediate-release, solid oral dosage forms»*. WHO Expert Committee on Specifications for Pharmaceutical Preparations (2006).

6.2 *In vitro* equivalence test

[1] http://www.fip.org/bcs

In vitro equivalence test should be carried out according Ministry of Health and Social Development of the Russian Federation «Guideline on investigation of bioequivalence», annex 4, 2008. The dissolution profile of the test and reference drug products should be measured under the same test conditions, i.e. apparatus, media volume, rotation speed, temperature (37 ± 0.5 ^{o}C).

6.2.1. Apparatus

Apparatus should meet the requirements of General Monograph 42-0003-04 «Dissolution Test», using paddle apparatus (75 rpm) or basket apparatus (100 rpm).

6.2.2. Dissolution media

In vitro equivalence test should be carried out using State Pharmacopoeia XII dissolution media pH 1.2, 4.5, 6.8. Other compendial media (USP, Ph. Eur, Int Ph) with same pH and buffer capacity are also acceptable. Dissolution media volume should be 900 ml or less, unless otherwise justified and authorized. Insolubility or instability of API in one or more of stated media should be interpreted and documented in study report. The usage of surfactants is not allowed for *in vitro* equivalence test.

6.2.3. Sampling

Samples should be taken at a sufficient number of intervals (not less than 3 time points excluding zero) to characterize the dissolution profile of the drug product completely. Typical time points are: 10, 15, 20, 30, and 45 min, time points 15 and 30 min are required to estimate dissolution characteristics (5.3) of drug product. The last time point should correspond to not less than 90 % of API released or saturation of dissolution process. Sampling of test and reference preparation should be performed simultaneously. Not less than twelve dosage units for each (test and reference) preparation should be studied to obtain statistically significant results.

6.2.4 Assay

Assay of released API should be performed by validated assay procedure. Decrease of media volume after sampling should be taken into account for calculations of % API released, or removed aliquot should be immediately replaced with equal volume of fresh medium at the same temperature to maintain constant total volume during the test.

6.2.5 Statistical treatment

Dissolution profiles similarity is evaluated by calculation similarity factor f_2 using formula:

$$f_2 = 50 * \log \{[1 + (1/n)\sum_{i=1}^{i=n} (R_t - T_t)^2]^{-0,5} * 100\}, \text{ where}$$

n – number of time points;

R_t – mean % of API released from reference preparation at time point *t*;

T_t – mean % of API released from test preparation at time point *t*.

Dissolution profiles are similar if:

- similarity factor f_2 value is 50 to 100;
- the percent relative standard deviation (% RSD) for mean % of API released for first time point is not more than 20 % and for other time points is not more than 10 %.

f_2 value = 50 corresponds 10% difference between the dissolution profiles. If dissolution profiles are completely equal, f_2 value is 100.

Not more than one mean value of more than 85% of API released for each (test and reference) preparation should be used for f_2 calculation.

Dissolution profiles are considered to be similar without statistical treatment if more than 85 % of API from each (test and reference) preparation released after 15 min.

Alternative methods to the f_2 statistic to demonstrate dissolution similarity are considered acceptable, if statistically valid and satisfactorily justified (e.g. f_1

calculation, or using of model-dependent methods), though f_2 calculation is considered to be sufficient.

6.3 Dissolution characteristics studies

Dissolution characteristics studies are carried out together with *in vitro* equivalence test according Ministry of Health and Social Development of the Russian Federation «Guideline on investigation of bioequivalence», annex 4, 2008 under the same test conditions, i.e. apparatus, media volume, rotation speed, temperature.

6.4. Excipients

Qualitative and quantitative composition of excipients containing in test and reference drug product should be estimated. Excipients used should not lead to differences between the test and reference drug product with respect to processes affecting absorption (e.g. by effects on gastrointestinal motility or interactions with transport processes), or which might lead to interactions that alter the pharmacokinetics of the API.

NOTE

Examples of excipients known to have caused bio*in*equivalence that would not have been predicted by dissolution testing include surfactants, mannitol and sorbitol.

Generally, the closer the composition of the test product and reference drug product with regard to excipients, the lower the risk of an inappropriate decision on waiver of *in vivo* bioequivalence studies and exchange them to *in vitro* equivalence test.

6.5. Risks assessment in terms of therapeutic index, therapeutic indications and adverse effects

Risks of therapeutic index, therapeutic indications and adverse effects of evaluated drug should be evaluated. If risks in cases of sub- or suprabioavaliability

are considered critical, conclusion on possibility of *in vitro* equivalence test should be made together with risk control conditions.

NOTE

For example, biovaiver monograph on ethambutole dihydrochloride (http://www.fip.org/files/fip/BPS/BCS/Monographs/Becker%202008.pdf) states that biowaiver can be recommended for immediate release solid oral dosage forms provided that the test product has a prescribers' information indicating the need for testing the patient's vision prior to initiating ethambutol therapy and regularly during therapy, because serious, dose-dependent ocular adverse effects may occur in case of supra-bioavaliability of ethambutol.

7. *In vitro* equivalence biowaiver criteria

7.1 Drug products containing BCS Class I API

In vitro equivalence biowaiver criteria for drug products containing BCS Class I API are:

- The dosage form is "rapidly dissolving" and the dissolution profile of the test product is similar to that of the reference product at pH 1.2, pH 4.5 and pH 6.8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm;
- If both the test and the reference dosage forms are "very rapidly dissolving" the two products are deemed equivalent and a profile comparison is not necessary.

7.2 Drug products containing BCS Class II API

In vitro equivalence biowaiver criteria for drug products containing BCS Class II API are:

- APIs is a weak acid with "*high*" solubility at pH 6.8 but not necessary at pH 1.2 and/or 4.5;

- the dosage form is “rapidly dissolving” in pH 6.8 buffer (only);
- the dissolution profile of the test product is similar to that of the reference product at pH 1.2, pH 4.5 and pH 6.8 buffer using the paddle method at 75 rpm or the basket method at 100 rpm.

For drug products containing Class 2 APIs with dose:solubility ratios of 250 ml or less at pH 6.8, the excipients should additionally be critically evaluated in terms of type and amounts, e.g. of surfactants, in the formulation. Further, if the C_{max} is critical to the therapeutic efficacy of the API, the risk of reaching an inappropriate biowaiver decision and its associated risks to public health and for individual patients may be deemed unacceptable.

7.3 Drug products containing BCS Class III API

In vitro equivalence biowaiver criteria for drug products containing BCS Class III API are:

- both the test and the reference dosage forms are “very rapidly dissolving” the two products are deemed equivalent and a profile comparison is not necessary.

The risks of reaching an inappropriate biowaiver decision for drug products containing BCS Class III API eligible for biowaiver need to be more critically evaluated when:

- the extent of absorption is lower (especially if F_{abs}< 50 %);
- the sites of absorption are restricted to the proximal regions in the gastrointestinal tract;
- the mechanism of absorption is subject to induction/competition.

7.4 Drug products containing BCS Class IV API

Drug products containing BCS Class III API are not eligible for biowaiver. Their interchangeability should be investigated in approved *in vivo* bioequivalence studies.

8. Report

In vitro equivalence test report for generic drugs according biowaiver procedure should include:

1. aims of study;

2. information about drug product: dose, manufacturer, batch, best before and status (Test or reference) for each preparation;

№	Drug product	Dose	Manufacturer	Batch	Best before	Test or reference preparation

3. dissolution kinetics study conditions;

4. assay procedure conditions;

5. results of study.

Results of dissolution kinetics study should be presented:

5.1. In table form with calculation of f_2 similarity factor if necessary.

	% dissolved, $\overline{X}$					
dissolution medium	pH 1,2		pH 4,5		pH 6,8	
time, min	drug product 1	drug product 2	drug product 1	drug product 2	drug product 1	drug product 2
10						
15						
20						
30						

45						
RSD, %						
≥ 85% in 15 min (yes/no)						
n						
f_2						

n – number of time points, taken into account for f_2 calculation.

5.2. In graphic form (dissolution profiles);

5.3. Summary table including data required for justified decision on waiver of *in vivo* bioequivalence studies and exchange them to *in vitro* equivalence test.

Characteristic	Value			Conclusion
Solubility	D_{max}, mg			
	S (pH 1,2), mg/ml			
	S (pH 4,5), mg/ml			
	S (pH 6,8), mg/ml			
	D/S (pH 1,2), ml			
	D/S (pH 4,5), ml			
	D/S (pH 6,8), ml			
Permeability	F_a, %			
	P_{eff} (*in vivo*)*, см/с			
	P_{eff} (*in situ*)**, см/с			
	P_{app} (*in vitro*)**, см/с			
Dissolution rate	pH	% dissolved		
		15 min	30 min	
	pH 1,2			
	pH 4,5			
	pH 6,8			
Risks associated with adverse effects				
Excipients	Test preparation		Reference preparation	

* - if data are available

* - these fields are not necessary, for supportive information only;

6. Conclusion on in vitro equivalence or inequivalence of test and reference drug product according biowaiver procedure.

Abbreviations

D_{max} – the highest dose (D, mg) of immediate release solid oral dosage form with Marketing Authorization in Russia

EMA – European Medical Agency

F_{abs} – fraction absorbed, %

FDA – U.S. Food and Drug Administration

P_{eff} – permeability coefficient (cm/s)

P_{app} – apparent permeability coefficient (cm/s)

S – API solubility (mg/ml) in aqueous solution with stated pH

WHO – World Health Organization