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Committee for Medicinal Products for Human Use (CHMP)

Compilation of individual product-specific guidance on demonstration of bioequivalence

Initial batch of individual guidance agreed by Pharmacokinetics Working Party	October 2013
Initial batch of individual guidance adoption by CHMP for release for consultation	24 October 2013
Start of public consultation for initial batch of individual guidance	15 November 2013
End of consultation (deadline for comments) for initial batch of individual guidance	15 February 2014
Respective batch - Agreed by Pharmacokinetics Working Party	See individual guidance
Respective batch - Adoption by CHMP	See individual guidance
Respective batch - Date for coming into effect	See individual guidance

Keywords	Bioequivalence, generics, product specific bioequivalence guidance, repaglinide, miglustat, erlotinib, dasatinib, emtricitabine-tenofovir

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Executive summary

The publication of product-specific guidance on demonstration of bioequivalence should facilitate the design of study programmes and allow a more transparent, consistent and robust evaluation of generic marketing authorisation procedures. Finalised guidelines for individual products, adopted by CHMP after a period of public consultation, will be published in the updated annex of this compilation of guidance every 6 months.

1. Introduction

The general European Union requirements for bioequivalence demonstration are laid out in the Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). In addition, the CHMP started in 2009 to publish positions addressing specific questions in relation to the requirements and assessment of bioequivalence studies (EMA/618604/2008). This document describes the regulatory view on product specific aspects related to the demonstration of bioequivalence, based on previous assessments of generic medicines. This should facilitate transparent, predictable and scientifically robust evaluation of future generic marketing authorisation procedures.

2. Scope

The aim of publishing product-specific guidance on demonstration of bioequivalence is to enable a consistent approach to the assessment of applications based on bioequivalence data, particularly generic applications, across all submission routes, i.e. submitted centrally, via the decentralised procedure or mutually recognition procedure, or nationally. Such product-specific guidance will facilitate the design of study programmes that meet the expectations of regulators in the European Union, hence allowing better predictability in terms of the assessment during the authorisation process.

3. Procedure

This guideline provides a compilation of product-specific guidance on the demonstration of bioequivalence for individual products authorised within the EU. The procedure for publication is as follows:

- DRAFT individual product-specific guidance on demonstration of bioequivalence will be published for a period of consultation on the EMA website. Comments received will be reviewed and discussed within the relevant scientific parties and committees and the draft product specific guidelines will be revised taking relevant comments into consideration.
- Finalised guidelines will be adopted by the CHMP and published in the updated Annex of this Compilation of guidance every 6 months.
- Comments on Comments will be published for each individual guideline together with the initial draft guideline.

4. Legal basis

The guidance is based on the general principles set out in the applicable overarching Guideline on the Investigation of Bioequivalence, and summarises in a standardised format the relevant design principles for bioequivalence demonstration.

5. Proposed timetable

Finalised guidelines will be adopted by the CHMP and published in the updated Annex of this guideline every 6 months.

6. Abbreviations

BCS Classification:	Biopharmaceutics Classification System
BE:	Bioequivalence
CHMP:	Committee for medicinal products for human use
PKWP:	Pharmacokinetic Working Party

Pharmacokinetic parameters:

$AUC_{(0-t)}$:	Area under the plasma concentration curve from administration to last observed concentration at time t;
C_{max}:	Maximum plasma concentration

7. References

Guideline on Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr**).

Concept paper on development of product-specific guidance on demonstration of bioequivalence (EMA/CHMP/423137/2013)

Procedure for European Union guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev. 1 corr)

Link to published Product-specific bioequivalence guidance on EMA website

Annex A: Product-Specific Bioequivalence Guidance for dasatinib; emtricitabine/tenofovir disoproxil; erlotinib; miglustat and repaglinide. Date for coming into effect: 01 June 2015.

Agreed by Pharmacokinetics Working Party	October 2014
Adopted by CHMP	20 November 2014
Date for coming into effect	1 June 2015

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A.1 Dasatinib film-coated tablets 20, 50, 70, 80, 100 & 140 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423718/2013

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Dasatinib may be considered a low solubility compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 140 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one single dose study

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and Cmax
	90 % confidence interval: 80.00 – 125.00

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

A.2 Emtricitabine/Tenofovir Disoproxil film-coated tablets 200 mg/245 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423726/2013

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☒ **I** ☒ **III** ☐ **Neither of the two** **Background:** Emtricitabine is considered a high solubility and permeability compound, tenofovir disoproxil is considered a high solubility and low permeability compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☒ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: Emtricitabine 200 mg and tenofovir disoproxil 245 mg **Background:** 200 / 245 mg is the only combination strength
	Number of studies: one single dose study

Analyte	☒ **parent** ☒ **metabolite** ☐ **both** **Background:** For emtricitabine the parent, for tenofovir disoproxil the metabolite (as tenofovir).
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t} and Cmax
	90 % confidence interval: 80.00 – 125.00

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

A.3 Erlotinib film-coated tablets 25, 100 and 150 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/418988/2013

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Erlotinib may be considered a low solubility compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 150 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one single dose study

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h} and Cmax
	90 % confidence interval: 80.00 – 125.00

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

A.4 Miglustat hard capsules - 100 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/422796/2013

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **Neither of the two** **Background:** The available data on solubility does not allow the BCS classification of miglustat. If the Applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, a BCS biowaiver could be applicable.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 100 mg **Background:** 100 mg is the only strength
	Number of studies: one single dose study

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	90 % confidence interval: 80.00 – 125.00

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).

A.5 Repaglinide tablets - 0.5, 1 and 2 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/422421/2013

Disclaimer:

This guidance should not be understood as being legally enforceable and is without prejudice to the need to ensure that the data submitted in support of a marketing authorisation application complies with the appropriate scientific, regulatory and legal requirements.

Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Repaglinide is a low solubility compound.
BE Study design	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed** As repaglinide can cause hypoglycaemia it is recommended to administer a glucose solution during the study.
	Strength: 2 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one single dose study

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	90 % confidence interval: 80.00 – 125.00

* As intra-subject variability of the reference product has not been reviewed to elaborate this product-specific bioequivalence guideline, it is not possible to recommend at this stage the use of a replicate design to demonstrate high intra-subject variability and widen the acceptance range of C_{max}. If high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

** This tentative BCS classification of the drug substance serves to define whether *in vivo* studies seems to be mandatory (BCS class II and IV) or, on the contrary, (BCS Class I and III) the Applicant may choose between two options: *in vivo* approach or *in vitro* approach based on a BCS biowaiver. In this latter case, the BCS classification of the drug substance should be confirmed by the Applicant at the time of submission based on available data (solubility experiments, literature, etc.). However, a BCS-based biowaiver might not be feasible due to product specific characteristics despite the drug substance being BCS class I or III (e.g. in vitro dissolution being less than 85 % within 15 min (BCS class III) or 30 min (BCS class I) either for test or reference, or unacceptable differences in the excipient composition).