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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
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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

This initial batch of individual guidance replaces Compilation of individual product-specific guidance on demonstration of bioequivalence (EMA/CHMP/736403/2014)

Keywords	Bioequivalence, generics, product specific bioequivalence guidance, repaglinide, miglustat, erlotinib, dasatinib, emtricitabine-tenofovir, carglumic acid, imatinib, memantine, oseltamivir, posaconazole
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Compilation of individual product-specific guidance on demonstration of bioequivalence

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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](#)



EUROPEAN MEDICINES AGENCY
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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



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)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two</p> <p>Background: Dasatinib may be considered a low solubility compound.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p>
	<p>Strength: 140 mg</p> <p>Background: Highest strength to be used for a drug with linear pharmacokinetics and low solubility.</p>
	<p>Number of studies: one single dose study</p>

Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} and C _{max}
	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 (CV_{intra} > 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

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)*

<p>BCS Classification**</p>	<p>BCS Class: <input checked="" type="checkbox"/> I <input checked="" type="checkbox"/> III <input type="checkbox"/> Neither of the two</p> <p>Background: Emtricitabine is considered a high solubility and permeability compound, tenofovir disoproxil is considered a high solubility and low permeability compound.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input type="checkbox"/> fasting <input checked="" type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p>
	<p>Strength: Emtricitabine 200 mg and tenofovir disoproxil 245 mg</p> <p>Background: 200 / 245 mg is the only combination strength</p>
	<p>Number of studies: one single dose study</p>

Analyte	<input checked="" type="checkbox"/> parent <input checked="" type="checkbox"/> metabolite <input type="checkbox"/> both Background: For emtricitabine the parent, for tenofovir disoproxil the metabolite (as tenofovir).
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} and C _{max}
	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 (CV_{intra} > 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)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two</p> <p>Background: Erlotinib may be considered a low solubility compound.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p>
	<p>Strength: 150 mg</p> <p>Background: Highest strength to be used for a drug with linear pharmacokinetics and low solubility.</p>
	<p>Number of studies: one single dose study</p>

Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-72h} and C _{max}
	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 (CV_{intra} > 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)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input type="checkbox"/> Neither of the two</p> <p>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.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p>
	<p>Strength: 100 mg</p> <p>Background: 100 mg is the only strength</p>
	<p>Number of studies: one single dose study</p>

Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} , C _{max}
	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 (CV_{intra} > 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:

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Requirements for bioequivalence demonstration (PKWP)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> Neither of the two</p> <p>Background: Repaglinide is a low solubility compound.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p> <p>As repaglinide can cause hypoglycaemia it is recommended to administer a glucose solution during the study.</p>
	<p>Strength: 2 mg</p> <p>Background: Highest strength to be used for a drug with linear pharmacokinetics and low solubility.</p>
	<p>Number of studies: one single dose study</p>

Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t} , C _{max}
	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 (CV_{intra} > 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).



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Annex B: Product-Specific Bioequivalence Guidance for carglumic acid; imatinib; memantine; oseltamivir; posaconazole. Date for coming into effect: 01 October 2015. **NEW**

Agreed by Pharmacokinetics Working Party	March 2015
Adopted by CHMP	16 March 2015
Date for coming into effect	1 October 2015



B.1 Carglumic acid dispersible tablets 200 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/422457/2013

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: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> neither of the two Background: carglumic acid may be considered a low solubility compound.
BE Study design <i>in case a BCS biowaiver is not feasible or applied</i>	single dose cross-over
	healthy volunteers
	<input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed
	Strength: 200 mg Background: 200 mg is the only strength.
	Number of studies: one single dose study dosing only one tablet/unit of 200 mg.
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both

	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-72h} , C _{max}
	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 (CV_{intra} > 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).

B.2 Imatinib hard capsules 50 and 100 mg, film-coated tablets 100 and 400 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423733/2013

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)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input type="checkbox"/> neither of the two</p> <p>Background: imatinib is a compound with complete absorption, but the available data on solubility does not allow its BCS classification. If the Applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, imatinib could be classified as BCS class I drug and a BCS biowaiver could be applicable.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p> <hr/> <p>healthy volunteers</p> <p><input type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input checked="" type="checkbox"/> either fasting or fed</p> <p>Either a fasting or a fed study is acceptable. The SmPC recommends intake in fed state to minimise the risk of gastrointestinal irritations. However, a single dose fasting study in healthy volunteers is feasible and preferred to increase the sensitivity to detect differences between products. A fed study is acceptable according to the Guideline on the investigation of bioequivalence based on SmPC recommendations.</p>

	<p>Strength: 400 mg</p> <p>Background: highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.</p>
	<p>Number of studies: one single dose study.</p>
Analyte	<p><input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both</p>
	<p><input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine</p>
	<p>Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no</p>
Bioequivalence assessment	<p>Main pharmacokinetic variables: AUC_{0-t}, C_{max}</p>
	<p>90% confidence interval: 80.00 – 125.00%</p>

* 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 (CV_{intra} > 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).

B.3 Memantine film-coated tablets 5, 10, 15 and 20 mg, oral solution 5 mg Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423734/2013

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	BCS Class: <input checked="" type="checkbox"/> I <input type="checkbox"/> III <input type="checkbox"/> neither of the two Background: memantine is a high solubility compound with complete absorption.
BE Study design <i>in case a BCS biowaiver is not feasible or applied</i>	single dose cross-over
	healthy volunteers
	<input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed
	Strength: any strength for the tablets. Background: Highest strength recommended. However, it is also possible to use the lower strengths for a drug with linear pharmacokinetics and high solubility.
	Number of studies: one single dose study.

	Other critical design aspects: the solution may be waived if the same amount of sorbitol is used as in the reference product.
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-72h} , C _{max}
	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 (CV_{intra} > 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).

B.4 Oseltamivir hard capsules 30, 45 and 75 mg, powder for oral suspension 6 mg/ml and 12 mg/ml Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423665/2013

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

<p>BCS Classification**</p>	<p>BCS Class: <input type="checkbox"/> I <input type="checkbox"/> III <input type="checkbox"/> neither of the two</p> <p>Background: oseltamivir is a compound with limited absorption, but the available data on solubility does not allow its BCS classification. If the Applicant generates the solubility data and classifies the drug according to the BCS criteria as highly soluble, oseltamivir could be classified as BCS class III drug and a BCS biowaiver could be applicable.</p>
<p>BE Study design</p> <p><i>in case a BCS biowaiver is not feasible or applied</i></p>	<p>single dose</p> <p>cross-over</p>
	<p>healthy volunteers</p>
	<p><input checked="" type="checkbox"/> fasting <input type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed</p>
	<p>Strength: 75 mg</p> <p>Background: highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.</p>

	Number of studies: one single dose study
	Other critical design aspects: the suspension may be waived if the same amount of sorbitol is used as in the reference product and if the powder for suspension can be proved to be in complete dissolution at the time of administration.
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-t_r} , C _{max}
	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 (CV_{intra} > 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).

B.5 Posaconazole oral suspension 40 mg/ml Product-Specific Bioequivalence Guidance

CHMP/PKWP/EMA/423719/2013

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: <input type="checkbox"/> I <input type="checkbox"/> III <input checked="" type="checkbox"/> neither of the two Background: posaconazole may be considered a low solubility compound with complete absorption.
BE Study design <i>in case a BCS biowaiver is not feasible or applied</i>	single dose cross-over
	healthy volunteers
	<input type="checkbox"/> fasting <input checked="" type="checkbox"/> fed <input type="checkbox"/> both <input type="checkbox"/> either fasting or fed High fat meal as defined in the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1; section 4.1.4).
	Strength: 400 mg Background: Most sensitive dose for an oral suspension of a low solubility drug.
	Number of studies: one single dose study

	Other critical design aspects: Significant intra-patient variability in the pharmacokinetic parameters of posaconazole has been reported. A replicate cross-over design study can be carried out as per the Guideline on the investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1; section 4.1.10).
Analyte	<input checked="" type="checkbox"/> parent <input type="checkbox"/> metabolite <input type="checkbox"/> both
	<input checked="" type="checkbox"/> plasma/serum <input type="checkbox"/> blood <input type="checkbox"/> urine
	Enantioselective analytical method: <input type="checkbox"/> yes <input checked="" type="checkbox"/> no
Bioequivalence assessment	Main pharmacokinetic variables: AUC _{0-72h} , C _{max}
	90% confidence interval: 80.00 – 125.00%

* If high intra-individual variability (CV_{intra} > 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).