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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

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, sirolimus, sorafenib, sunitinib, tadalafil, telithromycin, voriconazole, capecitabine, asenapine, entecavir, lenalidomide, prasugrel, rivaroxaban, sitagliptin, tacrolimus, ticagrelor, zonisamide.**

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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 is aimed at facilitating the design of study programmes and allowing more transparent, consistent and robust evaluation of generic marketing authorisation procedures. Finalised guidelines for individual products, adopted by the Committee for Medicinal Products for Human Use (CHMP) after a period of public consultation, are published twice-yearly.

1. Introduction

The general European Union (EU) 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). The present document describes the regulatory view on product-specific aspects related to the demonstration of bioequivalence, based on previous assessments of medicines.

2. Scope

The aim of publishing product-specific guidance 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 should facilitate the design of studies to meet the expectations of regulators in the EU. This in turn should allow better predictability in terms of 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 of individual guidance is as follows:

- A DRAFT is published for a period of public consultation on the European Medicines Agency website. Comments received are discussed within the Pharmacokinetic Working Party (PKWP) and the guidance is revised to take relevant comments into consideration.
- A final guidance is adopted by the CHMP and published within a new annex of this compilation.
- In addition, together with the initial draft guideline, an Overview of Comments is published for each individual guideline for which comments were received during the public consultation.

4. Legal basis

The product-specific guidance summarises in a standardised format the relevant design principles for bioequivalence demonstration. It is based on the general principles set out in the applicable ‘Guideline on the Investigation of Bioequivalence’.

5. Timetable

Finalised guidelines are adopted by the CHMP and published twice-yearly.

6. Abbreviations used

BCS Classification: Biopharmaceutics Classification System

BE: Bioequivalence

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

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

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 *in case a BCS biowaiver is not feasible or applied*	**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/serum** ☐ **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

Disclaimer:

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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 *in case a BCS biowaiver is not feasible or applied*	**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/serum** ☐ **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

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 *in case a BCS biowaiver is not feasible or applied*	**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/serum** ☐ **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

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:** 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 *in case a BCS biowaiver is not feasible or applied*	**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/serum** ☐ **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

Disclaimer:

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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 *in case a BCS biowaiver is not feasible or applied*	**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/serum** ☐ **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).

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

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

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:** carglumic acid may be considered a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **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	☒ **parent** ☐ **metabolite** ☐ **both**

	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, 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).

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

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **neither of the two** **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.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☐ **both** ☒ **either fasting or fed** 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.

	Strength: 400 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.
	Number of studies: one single dose study.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **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).

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

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☒ **I** ☐ **III** ☐ **neither of the two** **Background:** memantine is a high solubility compound with complete absorption.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **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	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, 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).

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

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☐ **neither of the two** **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.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 75 mg **Background**: highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.

	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	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **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).

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

Disclaimer:

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Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **neither of the two** **Background:** posaconazole may be considered a low solubility compound with complete absorption.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☒ **fed** ☐ **both** ☐ **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	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, Cmax
	90% confidence interval: 80.00 – 125.00%

* 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).

Annex C: Product-Specific Bioequivalence Guidance for sirolimus, sorafenib, sunitinib, tadalafil, telithromycin, voriconazole, capecitabine. Date for coming into effect: 01 November 2015.

Agreed by Pharmacokinetics Working Party	April 2015
Adopted by CHMP	May 2015
Date for coming into effect	1 November 2015

C.1 Sirolimus coated tablets 0.5, 1 and 2 mg, oral solution 1 mg/ml Product-Specific Bioequivalence Guidance

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:** sirolimus may be considered a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed** Both fasting and fed are necessary due to specific formulation characteristics. A high-fat meal is recommended.
	Strength: Tablets: 2 mg and 0.5 mg Oral solution: 1 mg/ml **Background:** Tablets: Highest strength to be used for a drug with linear pharmacokinetics and low solubility. For tablets dose proportionality has been demonstrated between 2 mg and 5 mg doses. 0.5 mg tablets are not strictly bioequivalent with the higher strengths in terms of Cmax.

	Oral solution: A bioequivalence study for the solution will be necessary unless the composition is qualitatively the same and quantitatively similar to the originator. If there is a quantitative difference in solubility enhancers, a bioequivalence study will be necessary if the differences cannot be justified by other data.
	Number of studies: Four studies: single dose fasting and fed at 2 mg and single dose fasting and fed at 0.5 mg.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-t}, Cmax
	90% confidence interval: 80.00 – 125.00% for Cmax and 90.00 - 111.11% for AUC_{0-t} **Background:** Sirolimus is a narrow therapeutic index drug.

C.2 Sorafenib film-coated tablets 200 mg Product-Specific Bioequivalence Guidance

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:** sorafenib is a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 200 mg **Background:** 200 mg is the only available strength.
	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **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).

C.3 Sunitinib hard capsules 12.5, 25, 37.5 and 50 mg Product-Specific Bioequivalence Guidance

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:** Sunitinib malate may be considered a high solubility compound with limited absorption.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 50 mg **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
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**

	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

C.4 Tadalafil film-coated tablets 2.5, 5, 10 and 20 mg Product-Specific Bioequivalence Guidance

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:** tadalafil is a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☐ fasting ☐ fed ☒ both ☐ either fasting or fed **Background:** The reference product can be taken with or without food according to the SmPC. Since, the specific formulation (e.g. particle size and excipients) is known to be critical to the performance of the formulation in fed conditions, it cannot be assumed that the impact of food will be the same regardless of formulation. Therefore, following the requirements for "specific formulation characteristics" described in the Bioequivalence Guideline, both fasted and fed state comparisons of test to reference formulations are required.
	Strength: 20 mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.

	Number of studies: two single dose studies (20 mg fasted and 20 mg fed)
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, 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).

C.5 Telithromycin film-coated tablets 400 mg Product-Specific Bioequivalence Guidance

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:** the available data does not allow the BCS classification of telithromycin. A BCS biowaiver could be applicable if the applicant generates data according to the BCS criteria to support its classification as BCS class I or III.
BE Study design *In case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 400 mg **Background:** 400 mg is the only available strength.
	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **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).

C.6 Voriconazole tablets 50, 200 mg and powder for oral suspension 40 mg/ml Product-Specific Bioequivalence Guidance

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:** voriconazole is a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 200 mg for the tablets 200 mg for the 40 mg/ml powder for the oral suspension **Background:** Highest strength to be used for a drug with linear pharmacokinetics and low solubility.
	Number of studies: one single dose study for tablets, one single dose study for the oral suspension.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**

	☒ **plasma/serum** ☐ **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).

C.7 Capecitabine film-coated tablets 150, 500 mg Product-Specific Bioequivalence Guidance

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:** absorption in humans is almost complete, but capecitabine is unstable in acidic medium. Therefore, the available data on solubility does not allow the BCS classification of capecitabine.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	patients
	☐ **fasting** ☒ **fed** ☐ **both** ☐ **either fasting or fed** Fed state recommended to minimise the risk of vomiting, for example standardized light meal for patients participating in the bioequivalence study.
	Strength: 500 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.
	Number of studies: one single dose study

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

* Since high intra-individual variability (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

Annex D: Product-Specific Bioequivalence Guidance for asenapine, entecavir, lenalidomide, prasugrel, rivaroxaban, sitagliptin, tacrolimus, ticagrelor, zonisamide. Date for coming into effect: 01 November 2016. NEW

Agreed by Pharmacokinetics Working Party	February 2016
Adopted by CHMP	April 2016
Date for coming into effect	1 November 2016

D.1 Asenapine sublingual tablets 5 and 10 mg product-4 specific bioequivalence guidance

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:** The active substance reaches the circulation primarily by absorption in the oral cavity, rather than by swallowing and absorption through the gastrointestinal tract. Therefore the product cannot be considered for a BCS based biowaiver.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers or patients in case of intolerability
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 5 and 10 mg **Background:** Non-linear pharmacokinetics of asenapine may be attributed to both limited solubility and limitations in the absorption capacity from the oral mucosa following sublingual administration. As per the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/Corr; section 4.1.6), for drugs with a less than proportional increase in AUC with increasing dose over the therapeutic dose range, bioequivalence should in most cases be established both at the highest strength and at the lowest strength

	(or a strength in the linear range), i.e. in this situation two bioequivalence studies are needed.
	Number of studies: two single dose studies
	Other critical design aspects: No fluids to be administered 1 hour before or 1 hour after dosing. Clear description of procedures for administering the product, mouth rinse and checks etc. Procedures should be representative of normal conditions of use e.g. no special measures to prevent swallowing of drug that would not be applicable in normal clinical use
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (CVintra > 30 %) is expected, the applicants might follow respective guideline recommendations.

D.2 Entecavir film-coated tablets 0.5 and 1 mg, oral solution 0.05mg/ml product-specific bioequivalence guidance

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 and absorption does not allow the BCS classification of entecavir. A BCS biowaiver could be applicable if the applicant generates data according to the BCS criteria to support its classification as BCS class I or III.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 1mg **Background:** Highest strength to be used for a drug with linear pharmacokinetics with no information on solubility available.

	Number of studies: Tablets: one single dose study. Oral solution: studies may be waived if the amount of maltitol used is very similar to the reference product.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.3 Lenalidomide hard gelatine capsules 2.5, 5, 7.5, 10, 15 and 25mg product-specific bioequivalence guidance

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:** Lenalidomide 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, lenalidomide could be classified as BCS class I drug and a BCS biowaiver could be applicable.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 25 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics with limited information on solubility available.

	Number of studies: one single dose study
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.4 Prasugrel film-coated tablets 5 and 10 mg product-specific bioequivalence 10 guidance

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:** Prasugrel may be considered a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 10 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** **Background:** The parent compound is not detected in human or animal plasma (or other biological

	matrix). Bioequivalence should be based on the first metabolite, R-95913.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.5 Rivaroxaban film-coated tablets 2.5, 10, 15 and 20mg product-specific bioequivalence guidance

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:** rivaroxaban may be considered a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☒ **fed** ☐ **both** ☐ **either fasting or fed** **Background:** since there is a different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths, fasting study should be conducted for the lower strengths, and fed study for the higher strengths
	Strength: 10 mg and 20 mg. **Background:** highest strength for a drug with linear pharmacokinetics and low solubility. Due to the different food effect at different strengths, studies with two strengths are required.

	Number of studies: two single dose studies. **Background:** One single dose study under fasting conditions with the 10 mg strength and one single dose study under fed conditions with the 20 mg strength
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.6 Sitagliptin film-coated tablets 25, 50 and 100 mg product-specific bioequivalence guidance

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:** sitagliptin is a high solubility compound with complete absorption.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 100 mg **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

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.7 Tacrolimus granules for oral suspension 0.2 and 1 mg product-specific bioequivalence guidance

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:** tacrolimus may be considered a low solubility compound.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 1 mg **Background:** highest strength to be used for a drug with linear pharmacokinetics and low solubility. Higher doses may be needed (multiple 1 mg doses) in case of poor bioanalytical methods.
	Number of studies: one single dose study.

Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☐ **plasma/serum** ☒ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** AUC_{0-72h}, C_{max}
	90% confidence interval: 80.00 – 125.00% for C_{max} and 90.00 - 111.11% for AUC_{0-72h} **Background:** tacrolimus is a narrow therapeutic index drug.

* 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.

D.8 Ticagrelor film-coated tablets 90mg product-specific bioequivalence guidance

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:** ticagrelor may be considered a low solubility compound with limited absorption.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 90 mg **Background:** 90 mg is the only strength.
	Number of studies: one single dose study.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**

	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).

D.9 Zonisamide hard capsules 25, 50 and 100 mg, orodispersible tablets 25, 50, 100 and 300 mg product-specific bioequivalence guidance

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:** zonisamide is a compound with complete absorption, but not highly soluble according to the BCS criteria. Thus, a BCS biowaiver is not applicable.
BE Study design *in case a BCS biowaiver is not feasible or applied*	**single dose** **cross-over**
	healthy volunteers
	☒ **fasting** ☐ **fed** ☐ **both** ☐ **either fasting or fed**
	Strength: 100 mg for the hard capsules, 300 mg for the orodispersible tablets **Background:** highest strength to be used for a drug with linear pharmacokinetics but not highly soluble
	Number of studies: one single dose study for each dosage form

	Other critical design aspects: intake without water for the orodispersible tablets.
Analyte	☒ **parent** ☐ **metabolite** ☐ **both**
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **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 (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).