Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

EMA product specific bioequivalence guidelines

General requirements for fasting vs fed studies

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BioBridges, Prague 26-27 September 2019

Disclaimer

The views expressed in this presentation are those of the speaker, and are not necessarily those of MHRA or EMA.

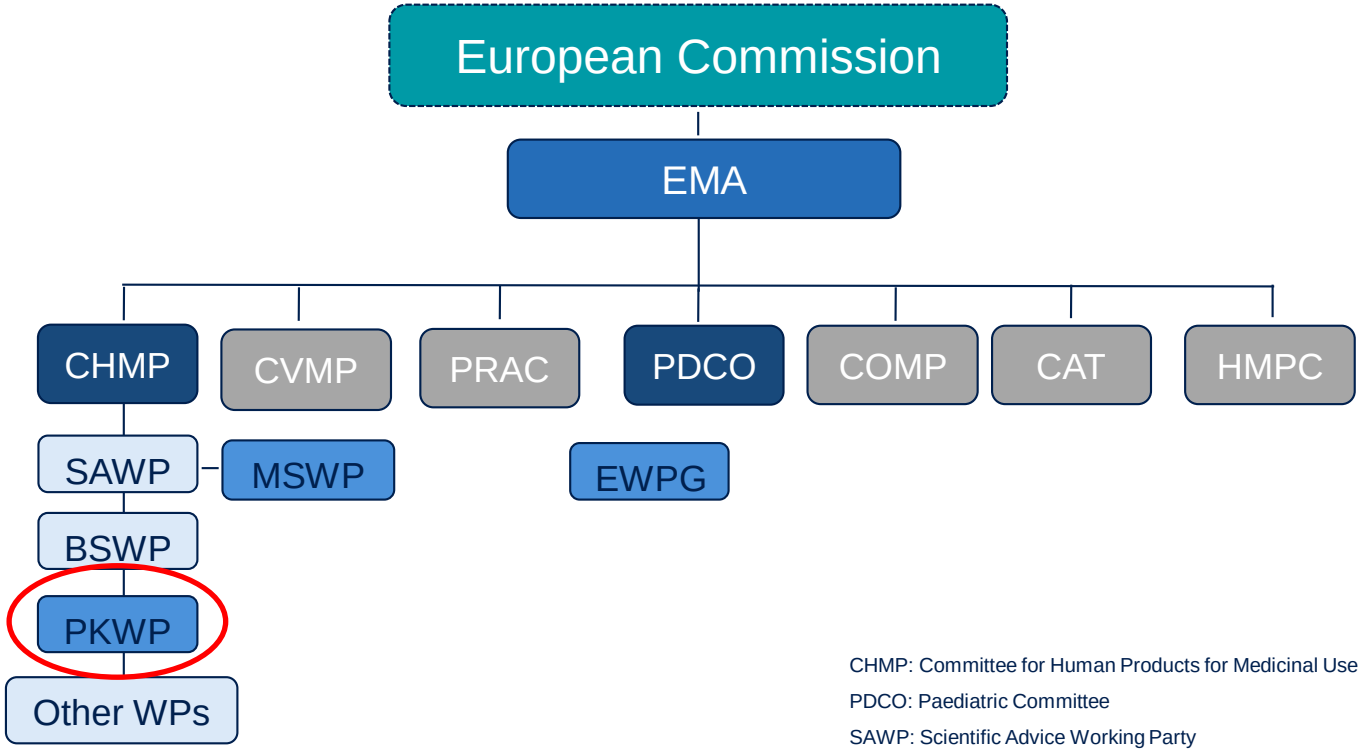
Overview

Guidelines 2018 - 2019

Product Specific Bioequivalence Guidelines (PSBGLs)

Regulatory requirements for PK fasting/fed studies

The European Regulatory System



CHMP: Committee for Human Products for Medicinal Use

PDCO: Paediatric Committee

SAWP: Scientific Advice Working Party

MSWP: Modelling and Simulation Working Party

EWG: Extrapolation Working Party

BSWP: Biostatistics Working Party

PKWP: Pharmacokinetics Working Party

Products 2018-2019

Guidelines currently on-going

- DDI
- Paediatrics
- ICH activities
- PSBGLs
- Modified release dosage forms
- Orally inhaled products

Guidelines finalised

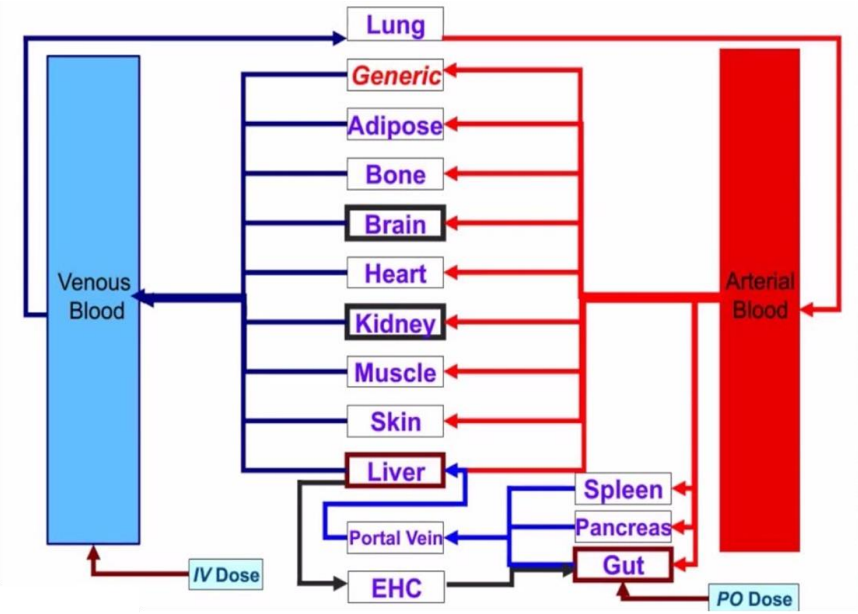
- PSBGLs (Batches 8 to 10)
- LALA
- PBPK

PBPK Guideline

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation



AIM: *To describe the expected content of PBPK modelling and simulation reports included in regulatory submissions, such as applications for authorisation of medicinal products, paediatric investigation plans and clinical trial applications. This includes the documentation needed to support the qualification of PBPK platform for the intended use and the evaluation of the drug model.*

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PSBGLs

Update 2018/2019

PSBGL

To help applicants meet the expectations of regulators in the EU, particularly for generic applications, across all regulatory submission routes, i.e. via the centralised, decentralised, mutual recognition or national procedures.

(…) The availability of PSBGL on the demonstration of bioequivalence will facilitate a transparent, predictable and scientifically robust framework for demonstration of bioequivalence in the interests of all stakeholders.

https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/product-specific-bioequivalence-guidance

PSBGL development

Product selection (CMDh)

Data collection (PKWP)

Draft adopted (CHMP)

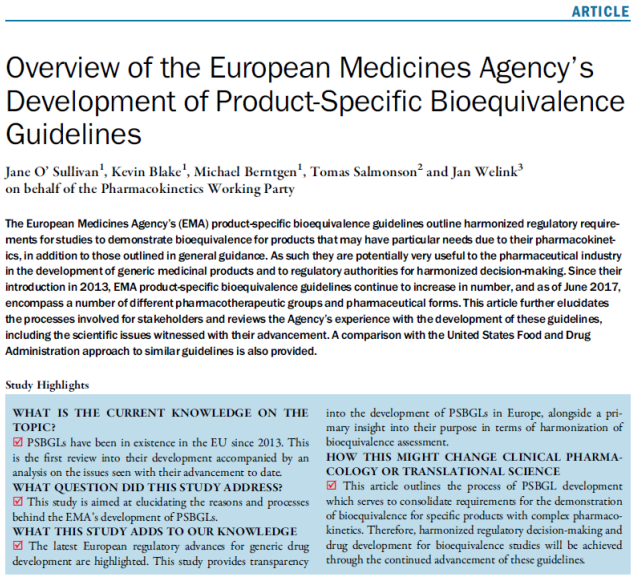
Draft sent to MAH (reference)

Public consultation

Revised draft (PKWP)

Final adoption (CHMP)

Final guideline (effective 6 months later)



ARTICLE

Overview of the European Medicines Agency's Development of Product-Specific Bioequivalence Guidelines

Jane O' Sullivan[1], Kevin Blake[1], Michael Berntgen[1], Tomas Salmonson[2] and Jan Welink[3]
on behalf of the Pharmacokinetics Working Party

The European Medicines Agency's (EMA) product-specific bioequivalence guidelines outline harmonized regulatory requirements for studies to demonstrate bioequivalence for products that may have particular needs due to their pharmacokinetics, in addition to those outlined in general guidance. As such they are potentially very useful to the pharmaceutical industry in the development of generic medicinal products and to regulatory authorities for harmonized decision-making. Since their introduction in 2013, EMA product-specific bioequivalence guidelines continue to increase in number, and as of June 2017, encompass a number of different pharmacotherapeutic groups and pharmaceutical forms. This article further elucidates the processes involved for stakeholders and reviews the Agency's experience with the development of these guidelines, including the scientific issues witnessed with their advancement. A comparison with the United States Food and Drug Administration approach to similar guidelines is also provided.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ PSBGLs have been in existence in the EU since 2013. This is the first review into their development accompanied by an analysis on the issues seen with their advancement to date.
WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This study is aimed at elucidating the reasons and processes behind the EMA's development of PSBGLs.
WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
☑ The latest European regulatory advances for generic drug development are highlighted. This study provides transparency into the development of PSBGLs in Europe, alongside a primary insight into their purpose in terms of harmonization of bioequivalence assessment.
HOW THIS MIGHT CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE
☑ This article outlines the process of PSBGL development which serves to consolidate requirements for the demonstration of bioequivalence for specific products with complex pharmacokinetics. Therefore, harmonized regulatory decision-making and drug development for bioequivalence studies will be achieved through the continued advancement of these guidelines.

Sullivan JO, Blake K, Berntgen M, Salmonson T, Welink J; Pharmacokinetics Working Party. Clin Pharmacol Ther. 2018 Sep;104(3):539-545.

PSBEGLs

Update 2018/2019

8th + 9th batches

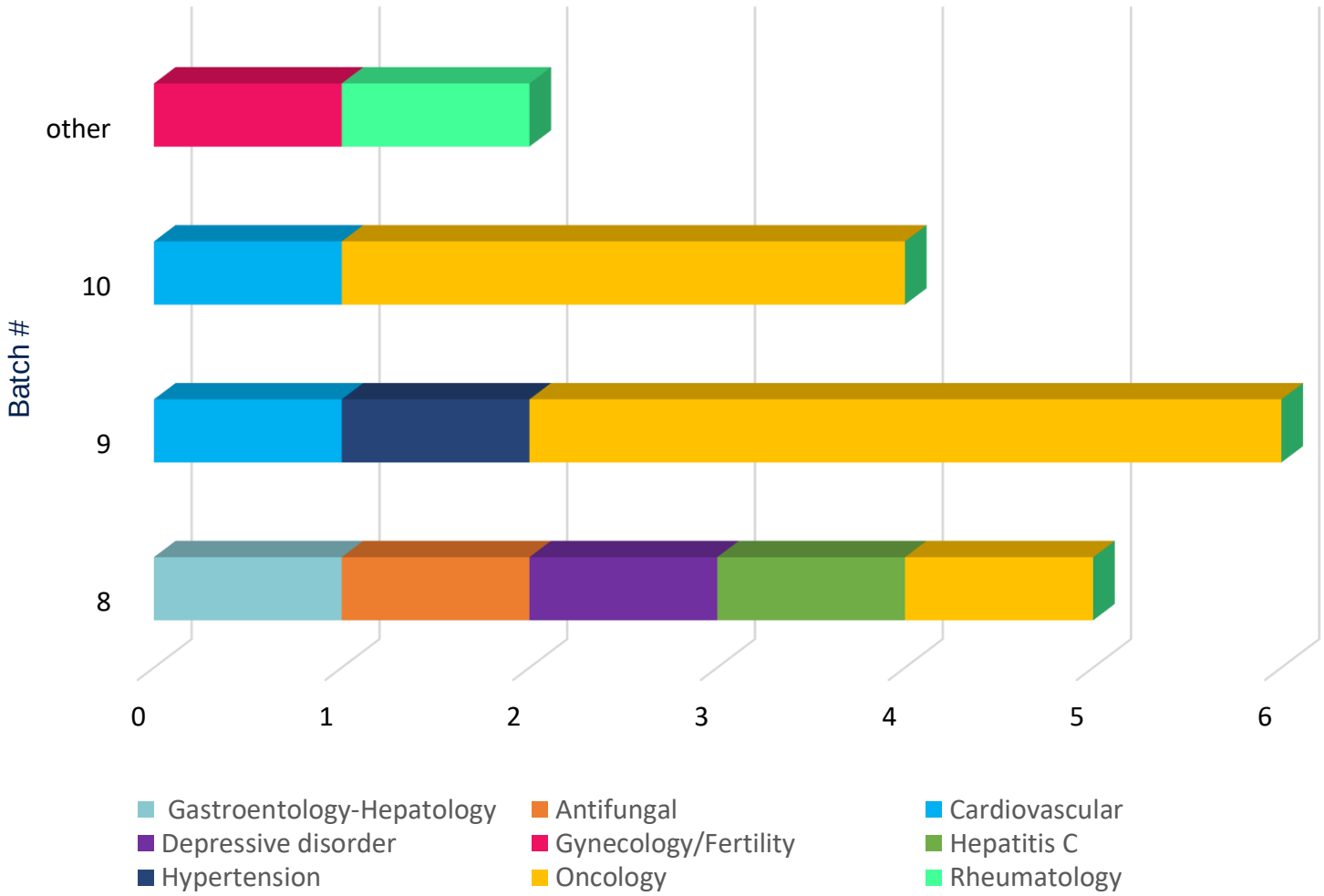
Final guideline adopted

10th batch

Public consultation finished/final adopted

Additional “ad hoc” products may be requested

PSBGLs 2018/19



PSBEGLs

Update 2018/19

Batch 8	Final guidelines				
Active Substance	**BCS class I or III**	**BE study design**	**Analyte**	**BE assessment**	**Note**
Cholic acid capsules 50 mg and 250 mg	Neither of them Low solubility	SD, crossover, HV, fed (not high fat) 250 mg	Both parent and metabolite (24h pre-dose baseline correction) Plasma/serum Achiral method	$AUC_{(0-t)}$, Cmax 90% CI: 80-125%	-
Posaconazole gastro-resistant tablet 100 mg	-	SD, cross over, HV, fasting and fed 100 mg	Parent Plasma/serum Achiral method	$AUC_{(0-t)}$, AUC_{inf}, C_{max} 90% CI: 80-125%	Delayed release
Ledipasvir/sofosbuvir film-coated tablet 90 mg/400 mg	Neither of them Low solubility	SD, cross over, HV, fasting ledipasvir 90 mg sofosbuvir 400 mg	Parent Plasma/serum Achiral method	Ledipasvir: AUC_{0-72h}, C_{max} Sofosbuvir: AUC_{0-t} and, C_{max} 90% CI: 80-125%	90 mg/ 400 mg is the only available combination strength
Vismodegib hard capsule 150 mg	Neither of them Low solubility	SD, cross over or parallel, HV, fasting 150 mg	Parent Plasma/serum Achiral method	AUC_{0-72h}, C_{max} 90% CI: 80-125%	-
Agomelatine tablet 25 mg	Class I high solubility complete absorption	SD, cross over, HV, fasting 25 mg	Parent Plasma/serum Achiral method	$AUC_{(0-t)}$, C_{max} 90% CI: 80-125%	Co-crystals may be acceptable for a biowaiver if BCS class I

PSBEGL

Update 2018/19

Batch 9	Final guidelines				
Active Substance	**BCS class I or III**	**BE study design**	**Analyte**	**BE assessment**	**Note**
Aliskiren film-coated tablet 150 mg and 300 mg	Class III	SD, crossover, HV, fasting and fed 300 mg (highest strength)	Parent Plasma/serum Achiral method	$AUC_{0\text{-}72h}$, C_{max} 90% CI: 80-125%	food effect with the reference product AUC increases more than proportionally with increasing dose
Octreotide depot powder and solvent for suspension for injection 10 mg, 20 mg and 30 mg	-	SD, parallel, HV 30 mg	Parent Plasma/serum Achiral method	Primary: $AUC_{(0\text{-}28d)}$, $AUC_{(28\text{-}56d)}$, $AUC_{(0\text{-}t)}$, $AUC_{(0\text{-}\infty)}$, C_{max}, C_t Secondary: $AUC_{(0\text{-}24h)}$, t_{ag}, C_{max} per partial AUC, C_{max} initial release 90% CI: 80-125%	Taking into account the difficulties in performing a MD study, as accumulation is not high and the SD profile is captured over a prolonged period, MD may be waived if the SD PK is well characterized.
Pegylated liposomal doxorubicin concentrate for solution 2 mg/ml	-	SD, cross over Standardized light meals rather than fasting may be needed due to patient's needs Any dose	Encapsulated and unencapsulated drug Plasma/serum Achiral method	$AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, C_{max}, partial AUCs (e.g. $AUC_{0\text{-}48h}$, $AUC_{48\text{-}tlast}$) 90% CI: 80-125%	No dose adjustments for toxicities during the study Unencapsulated concentrations measured by bioanalytical analysis and not by subtracting encapsulated from total drug.

PSBEGL

Update 2018/19

Batch 9	Final adopted				
Active Substance	**BCS class I or III**	**BE study design**	**Analyte**	**BE assessment**	**Note**
Apixaban film-coated tablet 2.5 and 5 mg	Incomplete absorption	SD, cross over, HV, fasting 5 mg	Parent Plasma/serum Achiral method	$AUC_{(0-t)}$, C_{max} 90% CI: 80-125%	Available data on solubility does not currently allow BCS classification. Linear PK in dose range 2.5 - 10 mg. If high solubility can be demonstrated, in principle any strength may be used.
Gefitinib film-coated tablet 250 mg	Neither of them Low solubility	SD, cross over, HV, fasting 250 mg	Parent Plasma/serum Achiral method	AUC_{0-72h}, C_{max} 90% CI: 80-125%	-

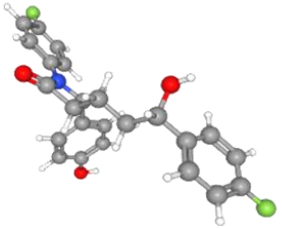
PSBEGL

Update 2018/19

Batch 10	Final adopted				
Active Substance	**BCS class I or III**	**BE study design**	**Analyte**	**BE assessment**	**Note**
Ezetimibe Tablet 10 mg	Neither of them Low solubility	SD, cross over, HV, fasting 10 mg	Both parent and metabolite Plasma/serum Achiral method	AUC_{0-72}, C_{max} 90% CI: 80-125%	Extensive pre-systemic metabolism
Cabozantinib Tablet 20, 40 and 60 mg Capsule 20 and 80 mg	Neither of them Low solubility	SD, cross over, HV, fasting Tablets 60 mg Capsules 80 mg	Parent Plasma/serum Achiral method	AUC_{0-72h}, C_{max} 90% CI: 80-125%	One SD study for each dosage form Tablets and capsules not BE
Alectinib Hard capsule 150 mg	Neither of them Low solubility	SD, cross over, HV, fed 150 mg	Parent Plasma/serum Achiral method	AUC_{0-72h}, C_{max} 90% CI: 80-125%	-
Palbociclib hard capsule 75 mg, 100 mg and 125 mg	Neither of them Low solubility	SD, cross over, HV, fed 125 mg	Parent Plasma/serum Achiral method	AUC_{0-72h}, C_{max} 90% CI: 80-125%	Linear PK

PSBGL - example

Ezetimibe

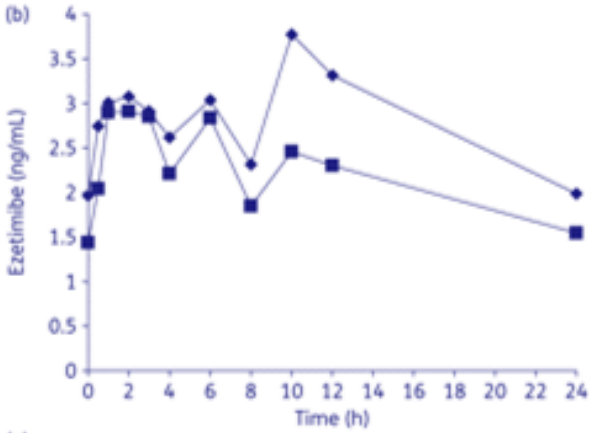


Extensive pre-systemic metabolism

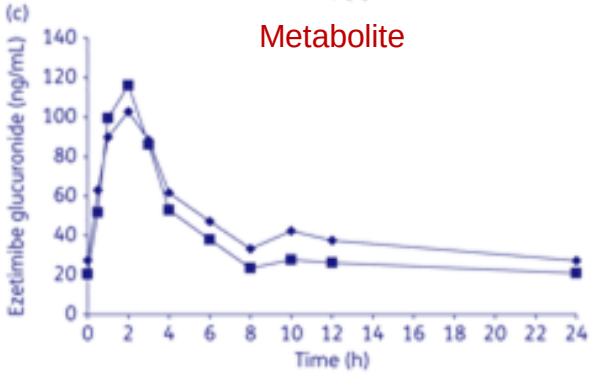
Ezetimibe-glucuronide is the major active metabolite

Because of extensive hepatic recirculation, the exposure to ezetimibe is less representative to evaluate absorption

Parent



Metabolite



Journal of Antimicrobial Chemotherapy, Volume 66, Issue 4, April 2011, Pages 885–889, https://doi.org/10.1093/jac/dkq546

PSBGL - example

Ezetimibe

Status: public consultation completed

B. Requirements for bioequivalence demonstration (PKWP)*

BCS Classification**	**BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two** **Background:** Ezetimibe is almost insoluble in aqueous medium.
Bioequivalence 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:** Only one strength available.
	Number of studies: One
Analyte	☐ **parent** ☐ **metabolite** ☒ **both** **Background:** Ezetimibe undergoes extensive pre-systemic metabolism; ezetimibe-glucuronide is the major active metabolite. Because of extensive hepatic recirculation, the exposure to ezetimibe is less representative to evaluate absorption.
	☒ **plasma/serum** ☐ **blood** ☐ **urine**
	Enantioselective analytical method: ☐ **yes** ☒ **no**
Bioequivalence assessment	**Main pharmacokinetic variables:** $AUC_{0\text{-}72h}$, C_{max} **Background/justification:** On total (parent + glucuronide metabolite together)
	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.

https://www.ema.europa.eu/en/documents/scientific-guideline/draft-ezetimibe-tablet-10-mg-product-specific-bioequivalence-guidance_en.pdf

PSBEGL

Update 2018/19

Additional products					
Active Substance	**BCS class I or III**	**BE study design**	**Analyte**	**BE assessment**	**Note**
Colchicine tablet 0.5 mg and 1 mg	Class III highly soluble with incomplete absorption	SD, cross over, HV, fasting 1 mg	Parent Plasma/serum Achiral method	C_{max}, $AUC_{(0-t)}$ 90% CI: 80.00– 125.00% for C_{max} 90.00-111.11% for $AUC_{(0-t)}$	As NTI drug, a BCS biowaiver is not possible. Adopted Sept 2019
Etonogestrel and ethinylestradiol vaginal delivery system 0.12mg/0.015mg/day	-	Cross over, HV (female), BE 28 days recommended. 1.2 mg/0.015 mg/day	Parent Plasma/serum Achiral method	C_{max}, $C_{\tau,ss=21d}$, $AUC_{(0-21d)}$, $C_{\tau,ss=28d}$, $AUC_{(0-28d)}$ 90% CI: 80-125%	Authorised duration of treatment is 3 weeks. The extended use up to 28 days should be considered. End of public consultation: Oct 2019

On-going discussions

PSBEGL Lapatinib

film-coated tablet 250 mg

Levothyroxine

4. Product-specific bioequivalence

Expand section | Collapse section

- 4.1 Bioequivalence studies for generic products containing clopidogrel. June 2009
- 4.2 Acceptance criteria for bioequivalence studies for losartan. July 2010
- 4.3 What are the requirements for demonstration of bioequivalence for ciclosporine generics? July 2010
- 4.4 Bioequivalence studies for generic application of omega 3 fatty acid ethylesters in a soft gelatine capsule. October 2013
- 4.5 What do I need to consider in a generic application for quetiapine lambda 200, 300, 400 mg prolonged release tablets? October 2013
- 4.6 Requirements for demonstration of bioequivalence for mycophenolate mofetil generics. January 2011
- 4.7 Demonstration of bioequivalence for ebastine. October 2013
- 4.8 CHMP request to PKWP for clarification on demonstrating bioequivalence of low dose acetylsalicylic acid gastro-resistant formulations in fixed dose combinations with substitution indication. December 2016
- 4.9 Ferric citrate coordination complex 1g film-coated tablets - product specific equivalence guidance December 2018
- 4.10 PKWP Q & A on pharmacokinetic (PK) characteristics of iron salts for oral use. Acceptable bridging/bioequivalence data. May 2019

Ferric citrate

Q&A 4.9

Iron component in ferric citrate coordination complex reacts with dietary phosphate in the GI tract and precipitates phosphate as ferric phosphate.

Insoluble and excreted in faeces, so the amount of phosphate absorbed from the GI tract is reduced.

Complex drug substance with standardised molar ratio

Drug substance similarity to be established based on comparative physico-chemical characterisations.

- ***Option 1 Biowaiver based on BCS classification***

Highly soluble substance with very low (<1%) systemic absorption (BCS class III).

BCS-based biowaiver may be applied (guideline on BE too).

Rapid dissolution is also acceptable for BCS III drugs without/with very low systemic bioavailability

- ***Option 2 In vitro studies***

If BCS-based biowaiver is not possible, in vitro phosphate binding studies comparing the test and reference products are considered acceptable surrogates for the assessment of efficacy, as ferric citrate coordination complex acts locally in the GI tract (Ref LALA guideline too)

1. Comparative in vitro equilibrium binding study (pivotal)
2. Comparative in vitro kinetic binding study

Final guideline

Revision

Even for final guidelines, revision is possible in line with new or emerging data – usually this comes through procedures (e.g. MAA through CMDh or through requests for SA)

Medicines & Healthcare products Regulatory Agency

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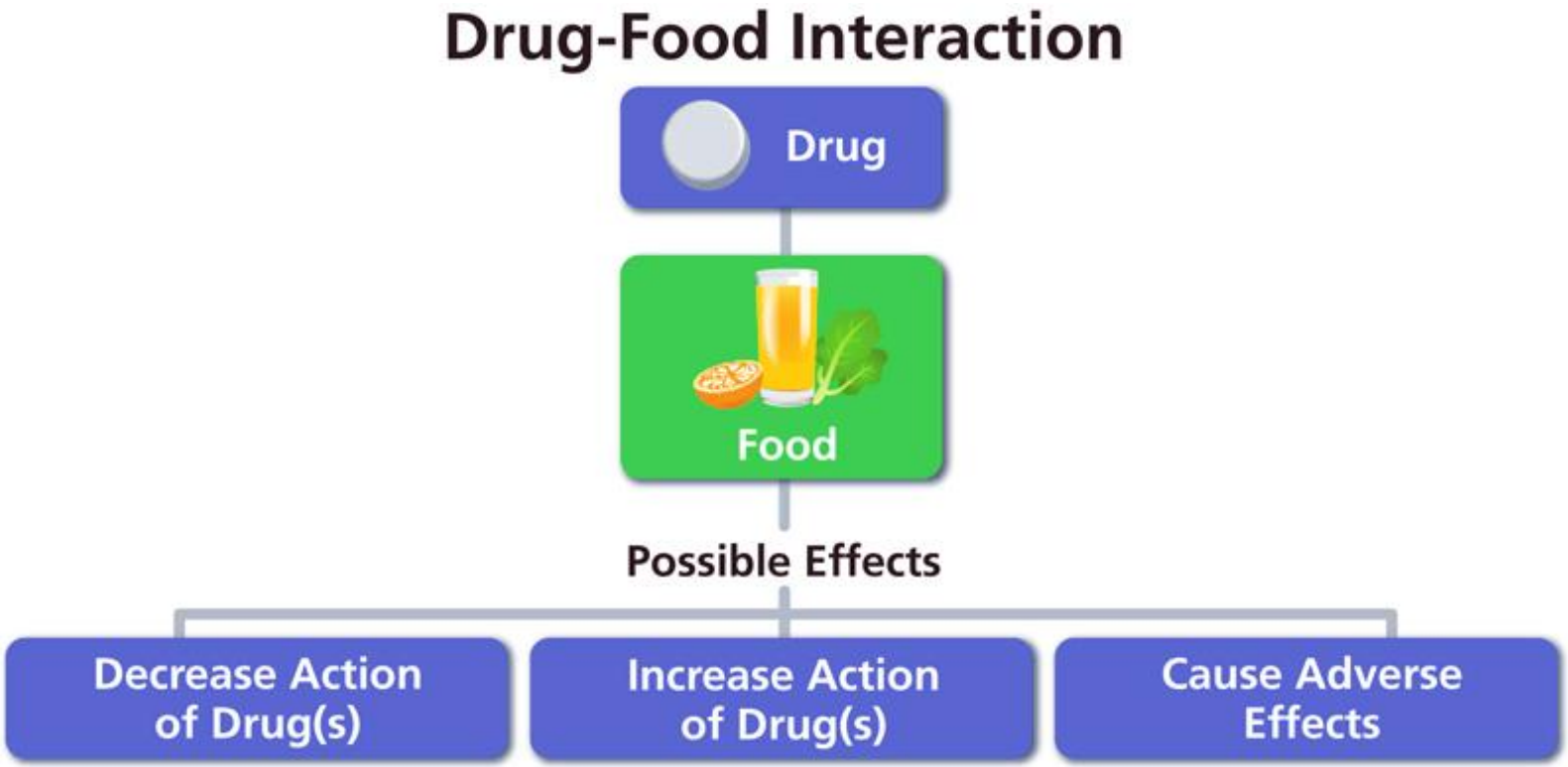
Drug-food interaction

Regulatory requirements for fasting/fed studies

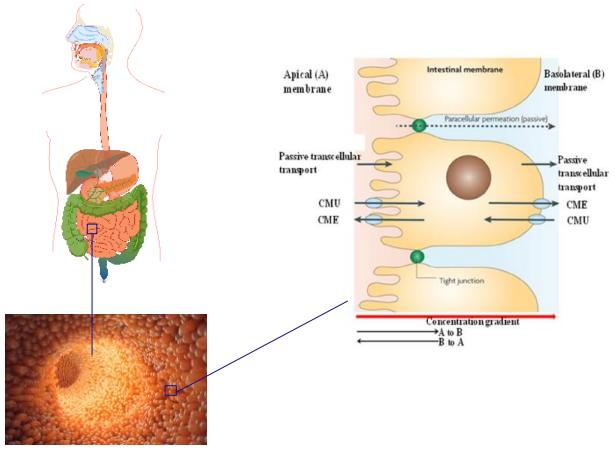
Food effect on drugs disposition

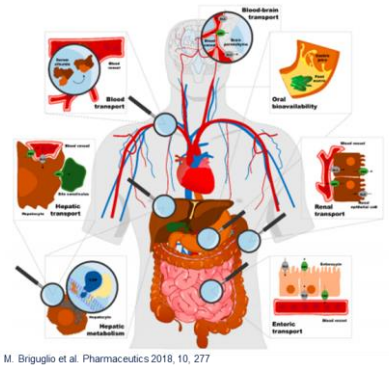


Drug-food interaction

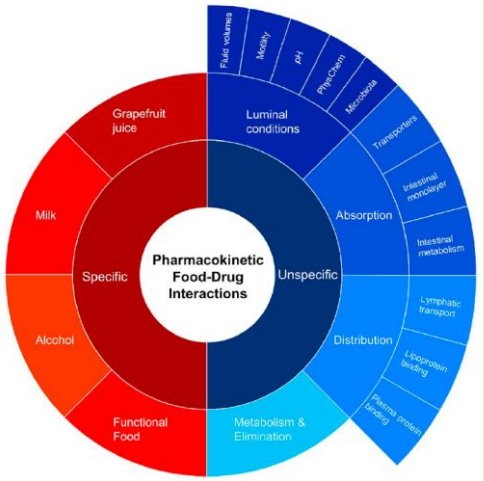
- Disintegration of the dosage form
- API dissolution
- Transport across the gut wall

Food may affect the absorbed drug fraction

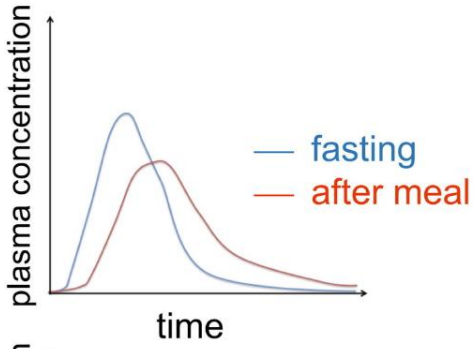




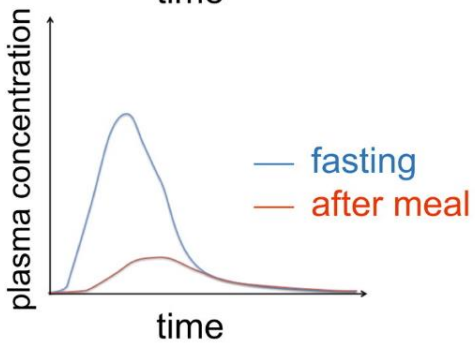
M. Briguglio et al. Pharmaceutics 2018, 10, 277



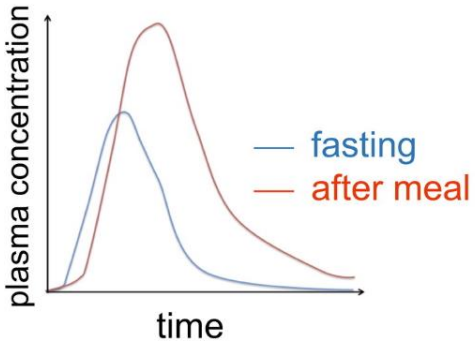
Drug-food interaction



- Similar AUC; reduced C_{max}; prolonged t_{max}
- May be due to prolonged gastric emptying



- Reduced absorption
- Physiochemical interaction with food components
- Possible interaction with transporters



- Increased absorption
- Effects on drug solubility
- Prolonged gastric residence time (different dissolution)
- Possible food interaction with transporters
- Food effect on drug metabolism (intestinal)

Koziolek M et al. Adv Drug Deliv Rev. 2016 Jun 1;101:75-88. doi: 10.1016/j.addr.2016.03.009. Epub 2016 Mar 29.

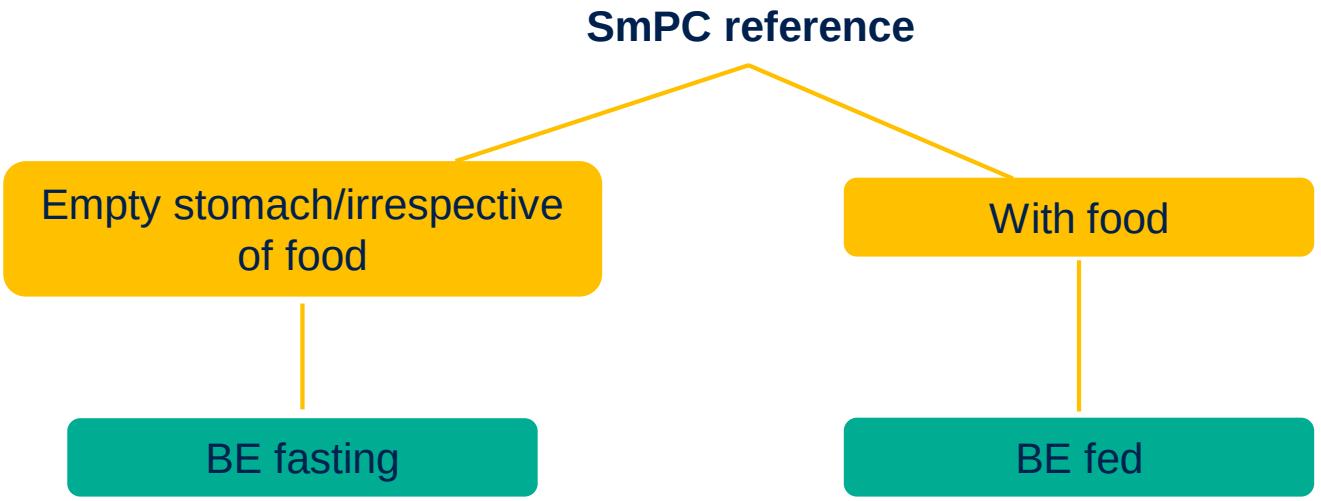
Requirements for fasting/fed studies

European guidelines

- Investigation on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)
- Investigation on the drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**)
- Investigation on the PK and clinical evaluation of modified release dosage forms (EMA/CPMP/EWP/280/96 Corr1)
- Demonstration of therapeutic equivalence for locally applied, locally acting products in the gastrointestinal tract (CPMP/EWP/239/95 Rev. 1, Corr.1*)
- PSBGLs
- Q&As

Immediate release formulation

In general, a BE study should be conducted under fasting conditions as this is considered to be the most sensitive condition to detect a potential difference between formulations.



- standardised diet, fluid intake and exercise
- At least 8 hours fasting prior to drug administration
- Water not allowed 1h before and after dosing/food not allowed at least 4h a.d.

- high-fat/high-calorie
- drug administration time based on originator's SmPC

Standard procedures

- SD administered with 240 ml of water after 10-h fasting period and 30 min after intake of a meal has been started;
- Except for the meal, subjects should be fasted for at least 4h a.d. and food intake should be standardised for at least 12h a.d.;
- High fat meal: 800-1000 kcal (500-600 kcal from fat and 250 kcal from carbs).

Food-drug interaction and any recommendation should adequately be addressed in the SmPC (sections 4.5 and 5.2 and cross-referred to the sections 4.2, 4.3 or 4.4).

Oral modified release

Food effect may be related to drug substance itself and/or formulation

MR NCE

- Early investigation in drug development (for efficacy/safety e.g. dose dumping)
- Usually 2-way crossover (MR fasting+fed)
  - **food effect**: is it formulation- or drug substance-related? (e.g.MR vs oral solution)
    - **food effect:** additional studies may be needed for dosing recommendations (different kinds of food; effect of meal at certain time before/after the drug, etc.)

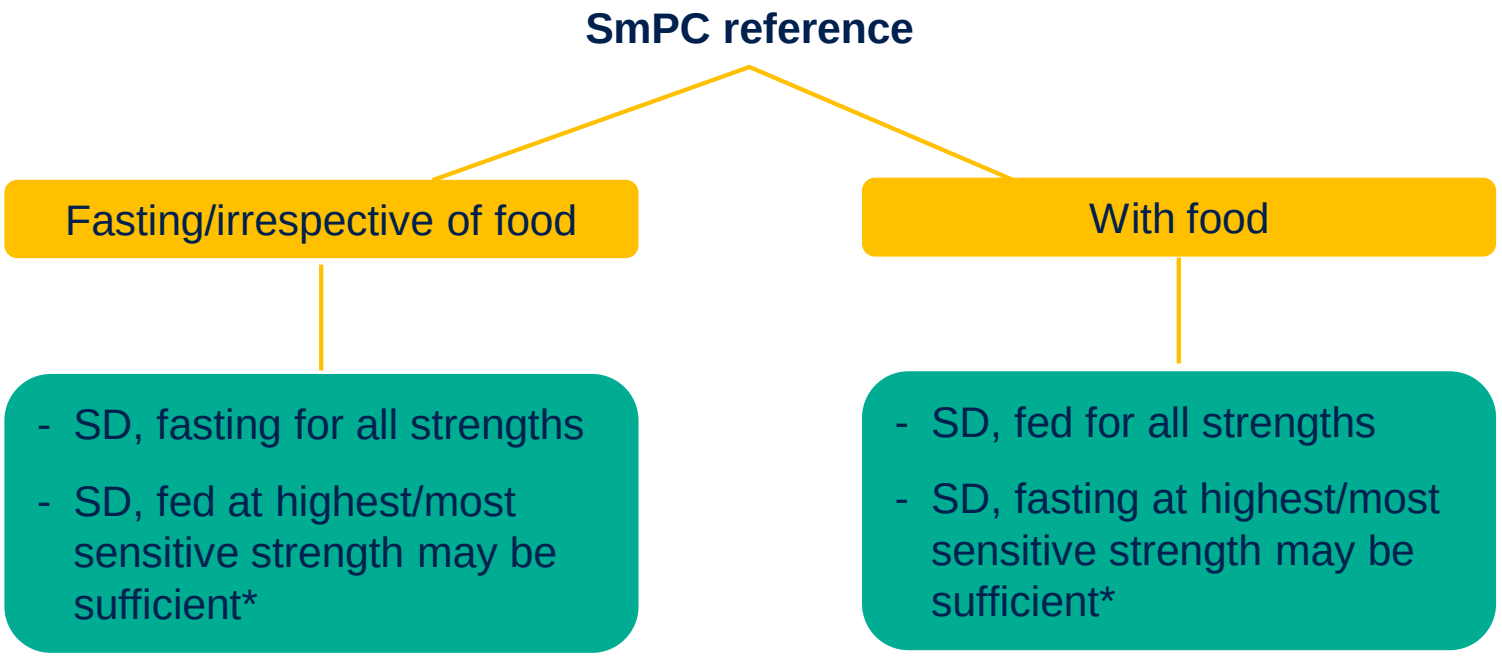
MR of authorised IR

- MR performance may be affected by food
- Usually SD and MD
- Study design depends on food effect for approved IR and available data for MR vs IR
  - **IR No food effect**: 2-way crossover - MR in fasting+fed
  - **IR Food effect:** 4-way crossover fasting +fed - MR vs IR useful to quantify the food effect on each formulation

- PK parameters: AUC, Cmax, shape of concentration–time profiles
- Generally highest strength to be tested. In some cases food effect at highest+lowest strengths to be investigated

Oral prolonged release

Food effect on in vivo performance should be comparable (BE) for both test and reference



MD is generally based on SmPC recommendation (intake in fasting or fed)

*if waiver criteria are met, others strengths may be waived. If not or different strengths have different shape, 2 strengths representing the most extreme difference should be tested

Prolonged release

risk of accumulation

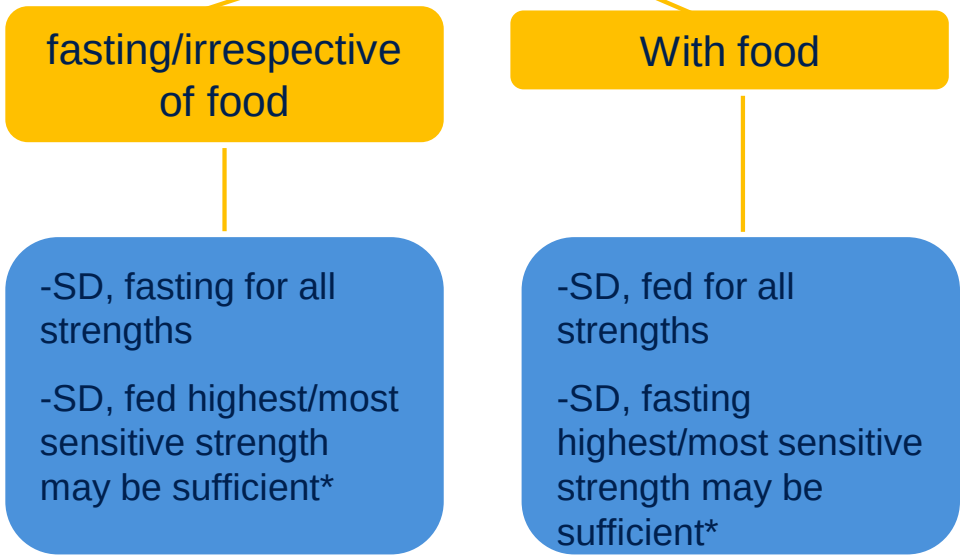
PR - accumulation			
	Single dose fasting	Single dose fed	Multiple dose
Cmax	yes	yes	no
AUC(0-t)	yes	yes	no
AUC(0-∞)	yes	yes	no
partialAUCs	no	no	no
Cmax,ss	no	no	yes
Cτ,ss	no	no	yes
AUC(0-τ,ss)	no	no	yes

PR - no accumulation			
	Single dose fasting	Single dose fed	Multiple dose
Cmax	yes	yes	no
AUC(0-t)	yes	yes	no
AUC(0-∞)	yes	yes	no
partialAUCs	yes	yes	no
Cmax,ss	no	no	no
Cτ,ss	no	no	no
AUC(0-τ,ss)	no	no	no

Oral delayed release

Food effect on in vivo performance should be comparable (BE) for both test and reference

SmPC reference



Delayed release			
	Single dose fasting	**Single dose fed**	**Multiple dose**
Cmax	yes	yes	no
$AUC_{(0-t)}$	yes	yes	no
$AUC_{(0-\infty)}$	yes	yes	no
$_{partial}AUCs$	no	no	no
$C_{max,ss}$	no	no	no
$C_{\tau,ss}$	no	no	no
$AUC_{(0-\tau,ss)}$	no	no	no

MD not needed!

*if waiver criteria are met, others strengths may be waived. If not or different strengths have different shape, 2 strengths representing the most extreme difference should be tested

Locally applied locally acting

IR formulations

if not BCS-based biowaiver

BE in fed and fasting may be surrogate of equivalence in efficacy and systemic safety because the sites of action is the site of absorption for drugs acting inside the GI membrane.

IR acting in the lumen/luminal side of the membrane

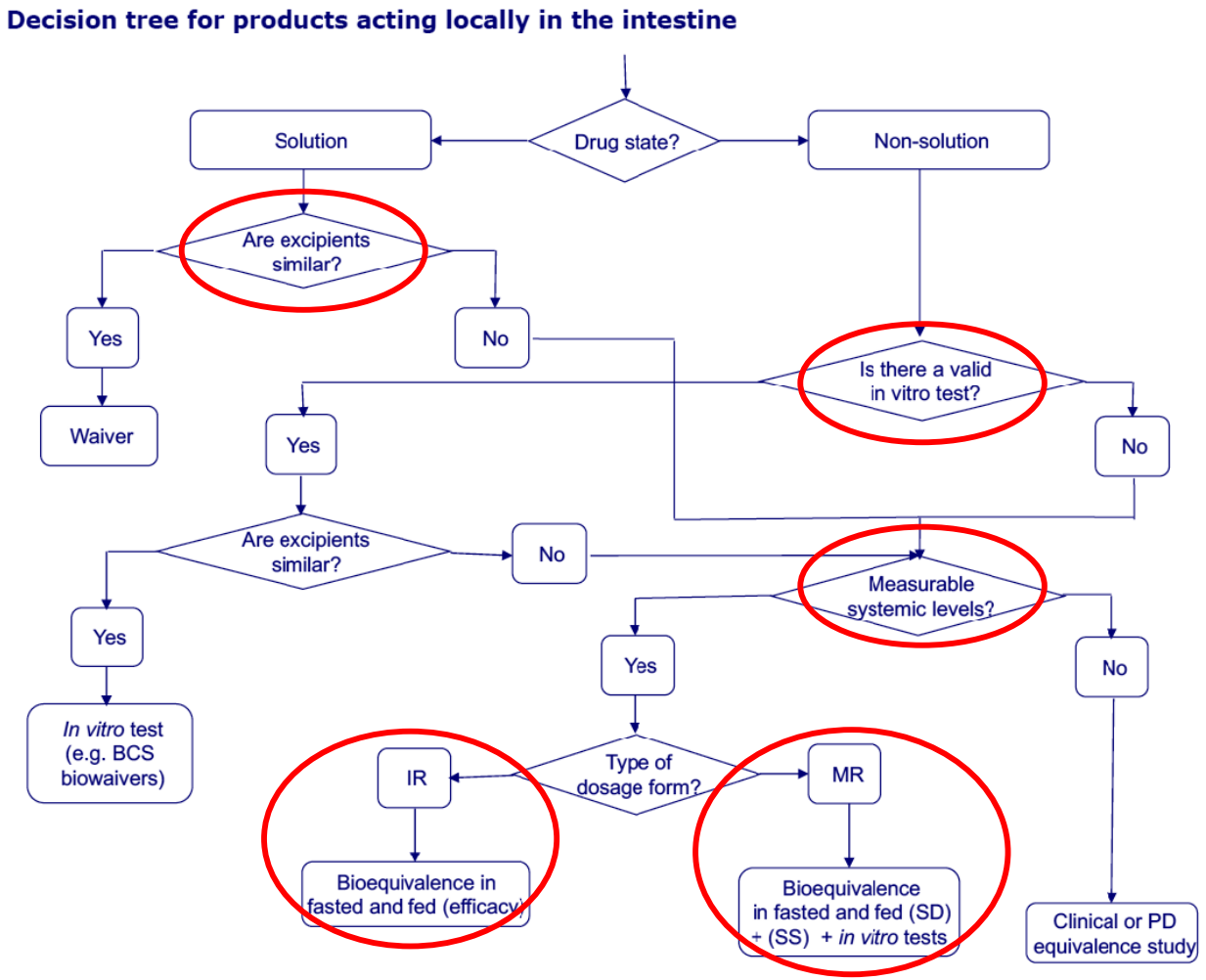
BE in fasting and fed may be surrogate of equivalence, if absorption is not saturated.

When rate and extent of absorption is comparable, distribution of drug within different zones of intestine are expected to be comparable.

Fasting and fed studies even for products to be taken in fasting only (generally low permeable and remain in intestinal lumen for a prolonged period - may interact with food during intestinal transit).

Locally acting MR formulations follow general criteria for MR

Locally applied locally acting



https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-equivalence-studies-demonstration-therapeutic-equivalence-locally-applied-locally-acting_en.pdf

Regulatory submission

Case study example

Compound X - modified release formulation

Important food effect on drug systemic exposure

→

Proposed SmPC/PI:

to be taken at bed time

→

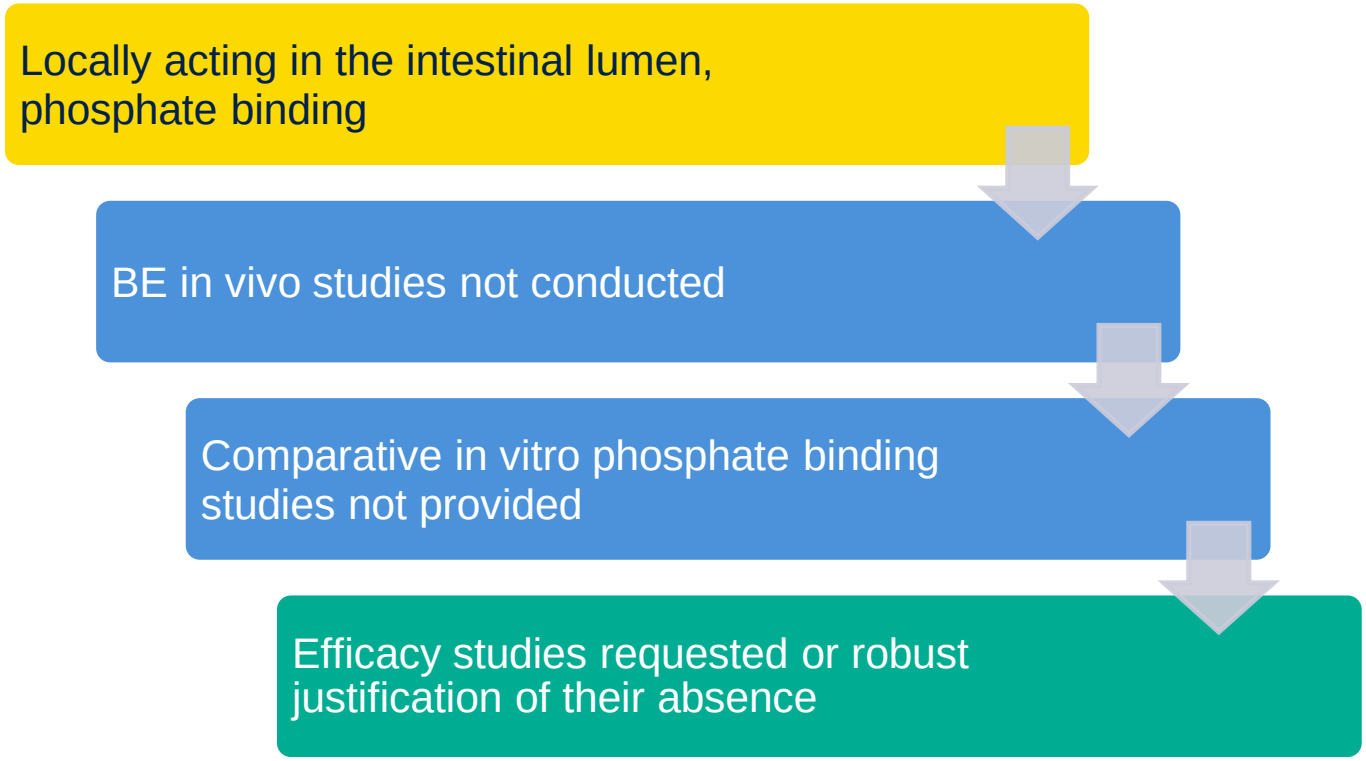
Requested SmPC/PI change:

to be taken several hours after meal ingestion

Regulatory submission

Case study example

Compound Z - modified release formulation



Regulatory submission

Case study example

Compound Y – immediate release formulation

SmPC: Absorption is unimpaired by food.

BCS-based biowaiver not acceptable

BE study conducted in fed condition as no food effect was claimed

The BE study should be conducted in fasting at highest strength

BCS classification

Dose ≤ 875 mg: Class I

Dose > 875 mg < 1000mg: Class II

Dose >1000 mg: Class IV

pH-dependent solubility expected to be limited at the highest dose.

Does not the SmPC recommend taking with food? then do it fasted!

Harmonisation

ICH
harmonisation for better health

ICH Reflection Paper
Endorsed by the ICH Assembly on 13 November 2018

ICH Reflection Paper

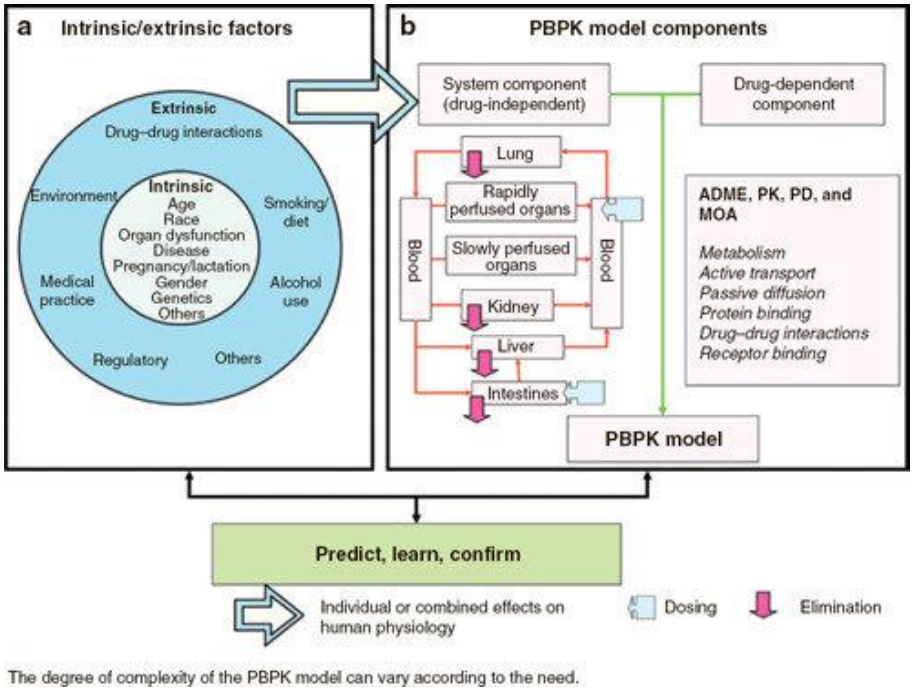
Further Opportunities for Harmonization of Standards for Generic Drugs[1]

Executive Summary

This reflection paper outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs. As part of this approach, this paper outlines recommendations to develop a series of ICH guidelines on standards for demonstrating equivalence (e.g., bioequivalence) for (1) non-complex dosage forms and (2) more complex dosage forms and products. To accomplish this work, it is proposed to establish a generic drug discussion group to assist in assessing the feasibility of harmonization of standards for generic drugs and to prioritize work areas.

PBPK modelling

A supporting tool



The degree of complexity of the PBPK model can vary according to the need.

Currently NOT accepted to replace in vivo study, but it might be a powerful tool to support/inform the investigation of food-drug interaction.

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Thank you