

Product specific bioequivalence guidelines – additional study with a proton pump inhibitor for generics

Carolien Versantvoort

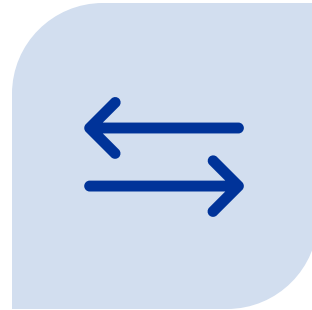
Senior clinical pharmacology assessor

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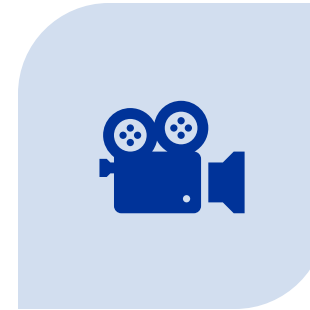
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New guideline for immediate-release solid oral dosage forms



Biggest change for generic development since initial EMA guideline (2010)



First in a foreseen ICH series, effective as of 25th of January



Recommendations for study design and data analysis

ICH M13A Guideline on bioequivalence for immediate-release solid oral dosage forms

Guideline on the investigation of bioequivalence (Rev 1)

Considerations regarding the implementation of ICH M13A on bioequivalence for immediate-release solid oral dosage forms

Product specific bioequivalence guidelines

Question & answer on the need for bioequivalence studies with acid reducing agents (ARAs)

Clinical pharmacology: Question & Answer

Into the future, the EMA Guideline on the investigation of bioequivalence will be replaced by the ICH series (ICH M13A, M13B and M13C) and withdrawn. EMA therefore commits to update this implementation document as the abovementioned harmonization efforts related to bioequivalence further advance.

Implementation Strategy

.....

“EMA is reviewing all of its existing [Product-specific bioequivalence guidance | European Medicines Agency \(EMA\)](#), (which are currently to be read in conjunction with the general requirements of [EMA Guideline on the investigation of bioequivalence](#)) to determine if they are compatible with the requirements of ICH M13A and to revise as needed.

...

CP-OEG, on behalf of MWP, started this process in October 2024

A total of 72 out of 91 product specific bioequivalence guidelines in scope

Review is a fundamental review of each guideline

Most of the guidelines are subject to a change

Major change: change is study requirements which would involve a public consultation

Minor change: textual changes (e.g. deleting reference to strength, adding the specific salt form)

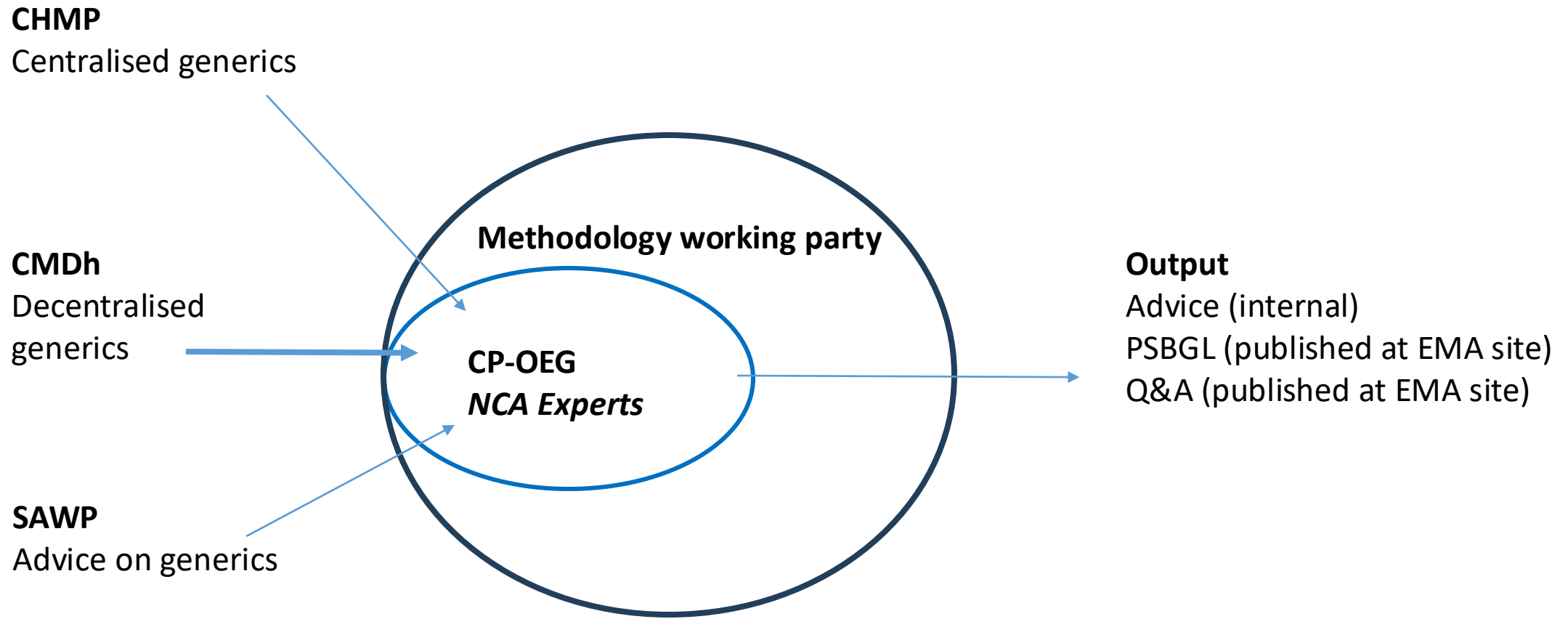
Product	Change (in line with M13A)
Aliskiren	Both fasting + fed study → Fasting study only
Dronedarone	High-risk product: Fed study only → Both fasting + fed study
Ledipasvir/sofosbuvir	High-risk product: Fasting study only → Both fasting + fed study
Sirolimus	Oral solution no high-risk: Both fasting + fed study → Fasting study only <i>Recommendation for tablets remains both fasting + fed study</i>

Three meetings with FDA to harmonise

– regional laws which may introduce few differences

Discussion ongoing on population (and dose) for oncology products

Review of the [Clinical pharmacology and pharmacokinetics: questions and answers | European Medicines Agency \(EMA\)](#) is ongoing



- “The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, **unless they differ significantly in properties with regard to safety and/or efficacy.**”
- “Biowaiver may be applicable when the active substance(s) in test and reference products are identical. Biowaiver may also be applicable if test and reference **contain different salts provided that both belong to BCS-class I** (high solubility and complete absorption; see sections III.1 and III.2).”

→ Drug substance is a different salt additional data are needed to ensure similar safety and efficacy. Guideline not very clear what the additional data should be.

Drug substance different salt – fasted and fed BE study needed or...?

2016-2018 Discussions amongst EU regulators:

Dabigatran etexilate, prasugrel, sunitinib, palbociclib,.....

The incidence of PPI use was highest for patients from gastroenterology (32.2%), hematology (31.8%), and oncology (29.2%). Eur J Clin Pharmacol. 2024

Additional study with acid reducing agents

Dabigatran etexilate mesilate

Interaction with PPIs is different from food effect.

Extensive drug substance and formulation development to evaluate interaction with acid reducing agents.

→ Selection of the formulation based on acceptable interaction with ARAs

→ An additional study under conditions of multiple day pre-treatment with a proton pump inhibitor (PPI) should be conducted in addition to the regular study under fasting conditions. (2018)

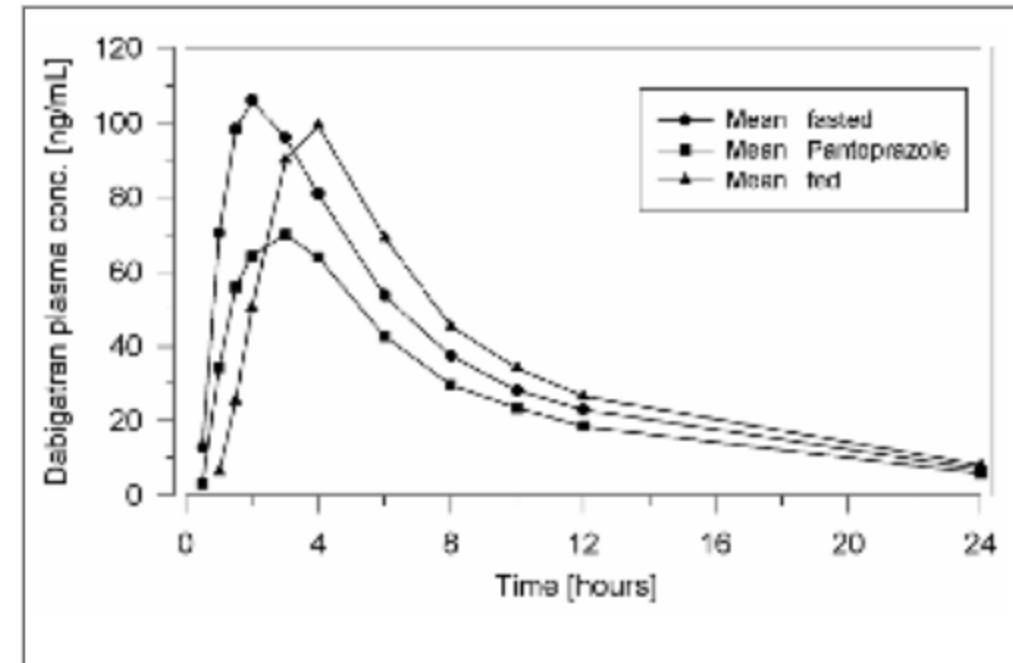


Figure 1. Mean plasma concentration-time profiles of dabigatran after single-dose administration of 150-mg capsules to healthy male volunteers in the fasted and fed states and when administered together with pantoprazole (40 mg bid).

Stangier et al., Journal of Clinical Pharmacology, 2005

Palbociclib capsules formulation (innovator)

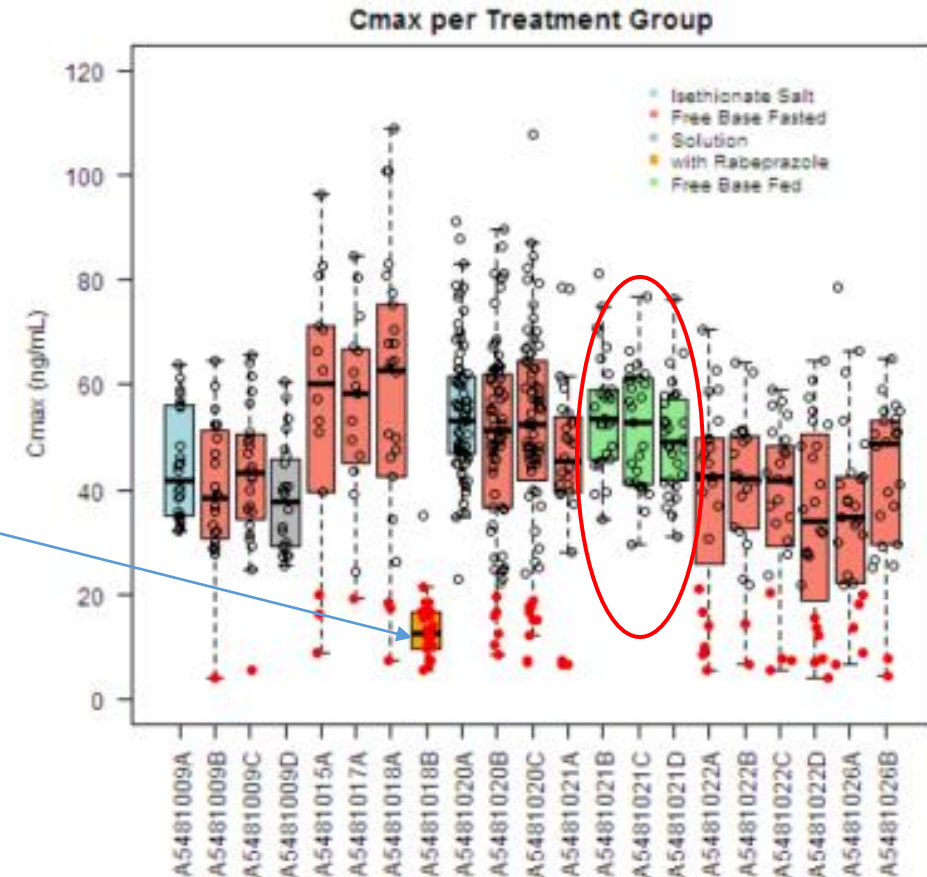
Capsules:

Rabeprazole gave rise to a marked (**61%**) reduction in palbociclib exposure during fasting conditions due to the pH dependent solubility of palbociclib. However, under fed conditions (moderate-fat meal), the effect was only a 13% decrease and therefore not clinically relevant.

Fed conditions variability less, no low-liers as under fasted conditions. No apparent low-liers with palbociclib salt or solution.

→ Capsules with a meal

→ Commitment for development of a new formulation with less inter-and intra subject variability



Ibrance capsules EPAR EMA

Palbociclib switch from capsules formulation to film-coated tablets

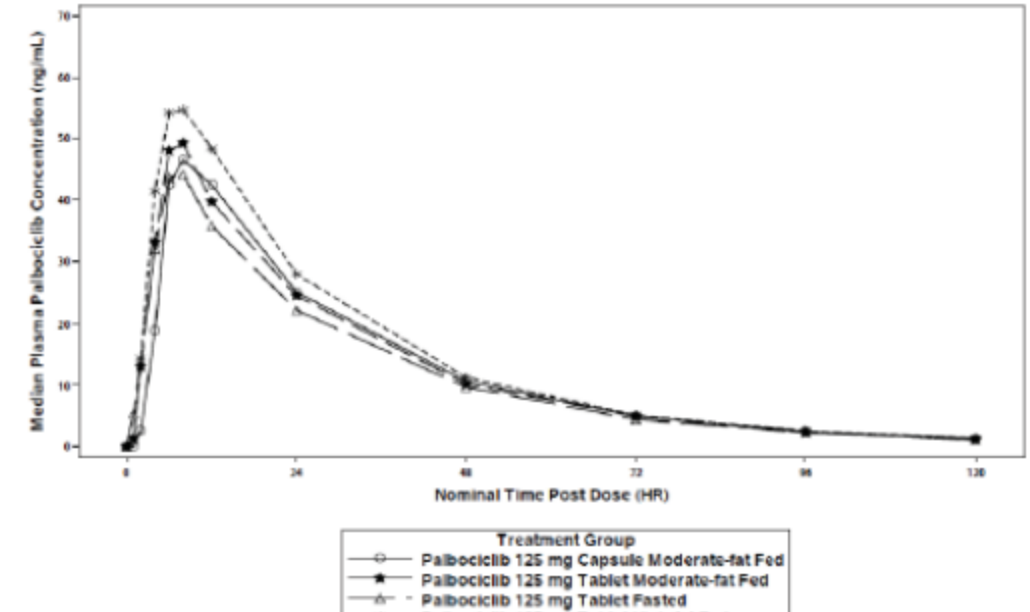
Additional study with acid reducing agents

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Tablet formulation: contains pH-modifying excipient

Bioequivalence study 125 mg capsules vs 125 mg tablets under fasted and moderate-fat fed conditions

Study with tablet formulation under fasted conditions with rabeprazole



Pharmacokinetic Parameter (Unit)	Adjusted Geometric Means Rabeprazole + Palbociclib (Test)	Adjusted Geometric Means Palbociclib Alone (Reference)	Ratio (Test/Reference) of Adjusted Means ^a	90% CI for Ratio ^a
AUC _{inf} (ng·hr/mL)	1408.32	1322.79	106.47	(99.22, 114.24)
AUC _{last} (ng·hr/mL)	1360.95	1278.91	106.42	(99.11, 114.25)
C _{max} (ng/mL)	44.82	45.99	97.45	(90.44, 104.99)

a. The ratios (and 90% CIs) are expressed as percentages.

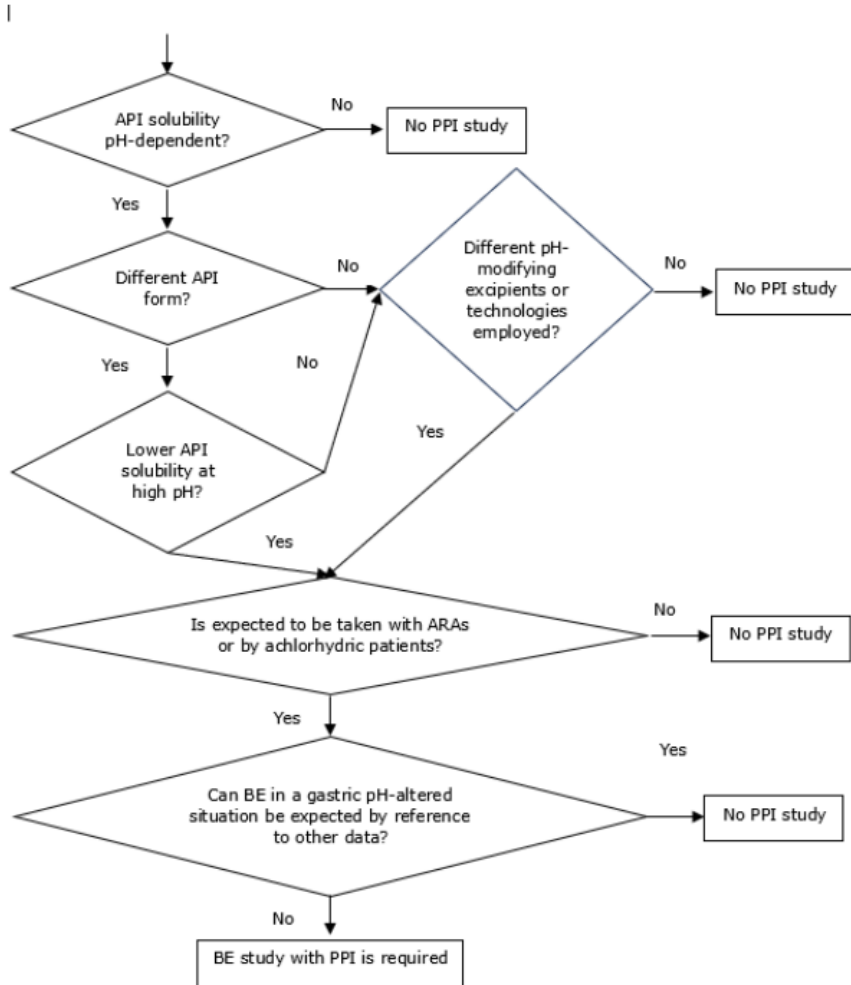
PSBGL palbociclib tablets:

- 1) Fasted study
- 2) PPI study unless.....

- “The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, **unless they differ significantly in properties with regard to safety and/or efficacy.**”
- “Biowaiver may be applicable when the active substance(s) in test and reference products are identical. Biowaiver may also be applicable if test and reference **contain different salts provided that both belong to BCS-class I** (high solubility and complete absorption; see sections III.1 and III.2).”

EMA Question & answer on the need for bioequivalence studies with acid reducing agents (ARAs)

Decision Tree



EMA product-specific bioequivalence guidelines have been published referencing to the salt, polymorphic form and hydration/solvation state of the drug substance used in the formulation of the reference medicinal product with its specific biopharmaceutical characteristics.

An additional bioequivalence study with concomitant treatment of a Proton-Pump Inhibitor (PPI) as an acid-reducing agent is necessary in principle :

- The products under comparison contain an active substance with pH-dependent solubility in the range between pH 1.2 and 6.8; and:
- There are qualitative or quantitative differences in the pH-modifying excipient(s), significant differences in manufacturing process affecting the pH-dependent dissolution or differences in the salt, hydration/solvation state or polymorphic form with a different pH-dependent solubility.

- a) The **pH-solubility profile** in the pH range from 1.2 to 6.8.
- b) Effect of the **PPI** on the absorption from the **reference medicinal product**.
- c) Excipient **composition** and the **manufacturing process** affecting the pH-dependent dissolution in the case of formulations designed to avoid the impact of the pH on drug absorption.
- d) In vitro **dissolution profiles** in the pH range from 1.2 to 6.8.

If the pH-solubility profile is similar and no pH-modifying excipients or special technologies are used, the study could be waived.

If it is known that PPIs do not affect the absorption of the API form employed in the reference medicinal product and the new form of the active substance exhibits a higher solubility, the study could be waived.

“...in certain situations, an additional BE assessment with concomitant treatment of a pH-modifying drug product would generally be necessary if all of the following criteria are met:

- a) a drug substance with **pH-dependent solubility** in the pH range of 1.2 - 6.8.
- b) The drug product is expected to be taken **with acid reducing agents**, e.g., proton pump inhibitors.
- c) There are **qualitative or quantitative differences in the pH modifying excipient(s)**, significant differences in manufacturing process that may affect drug absorption due to gastric pH differences, **or differences in the salt or polymorphic** form that possess a different pH dependent solubility.

————→ no PPI study needed when the pH-dependent soluble drug substance is identical and ‘simple’ immediate release formulation

In line with EMA Question & answer on the need for bioequivalence studies with acid reducing agents (ARAs)

Applicants may provide a scientific justification to demonstrate that a BE study in a gastric pH-altered situation may not be needed. Such a justification should be based on the totality of evidence referring to the pH-solubility profile of the drug substance, impact of excipients, formulation and manufacturing design, e.g., formulation designed to overcome pH effects, extent of the differences between the test and comparator products, and comparative dissolution testing at multiple pHs.

Modelling and simulation, e.g., appropriately validated PBPK modelling or semi-mechanistic absorption models, and virtual BE simulation, may be used to further assess the risk of bioinequivalence

- Use of more physiological related dissolution solutions
- Absorption kinetics
- Tiny-TIM
- PBPK modelling
-

Challenges multiple physiological changes over time by PPIs

- Stomach pH not constant during day
- Timing of drug and PPI to mealtimes
- Scale of stomach pH and emptying changes
- PPI may be inhibitor of enzymes and transporters

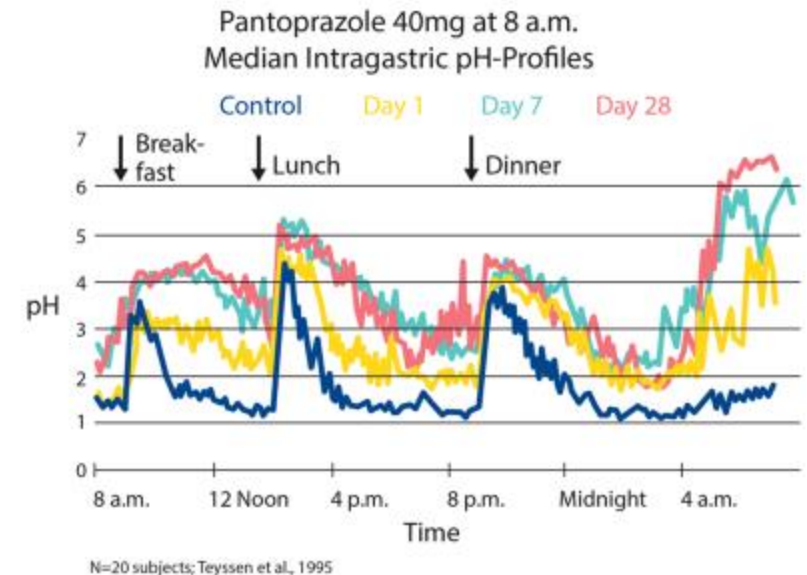


Fig. 13 Intra-gastric pH profile with PPIs before breakfast. Arrow show pH at night <2.0. Reprinted with permission from Macmillan Publishers Ltd: Harder et al. [61]

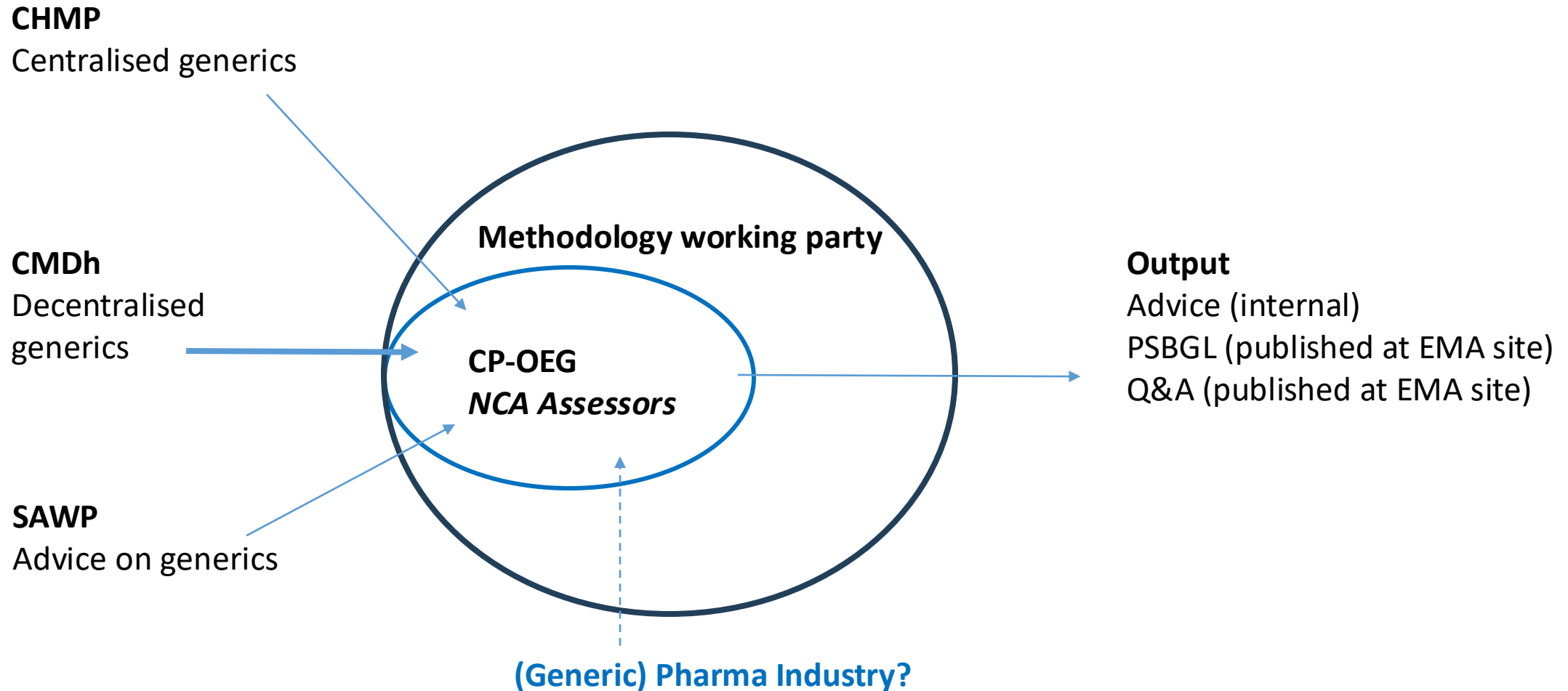
- **Draft-ICH-M15 (2025)**
- **Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation (2019)**

Description of mechanism, physiological conditions of the model and the assumptions made

- Objectives
- Data collection and description of the variables
- Formulation composition: pH modifying excipients, excipients that may influence the absorption
- Dataset: validation of the model with several medicinal products with and without impact of PPI on the bioavailability.
- Acceptance criteria considering the reference product
- Uncertainty of the model – clinical impact if not correct predicted.
- Does the medicinal product fall within the validated model space?

Product specific bioequivalence guidance

Question to the audience





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Thank you