Medicines & Healthcare products Regulatory Agency

# ICH M13A comments and examples from authorised medicinal products

Dr Mary Malamatari

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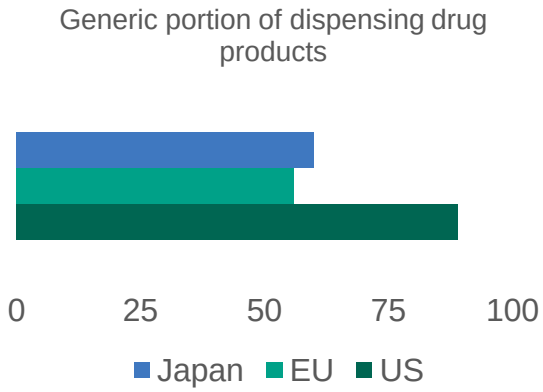
# Disclaimer

Any opinions expressed in this presentation are my own, are not necessarily shared by other assessors at the MHRA, and cannot be considered to be UK policy

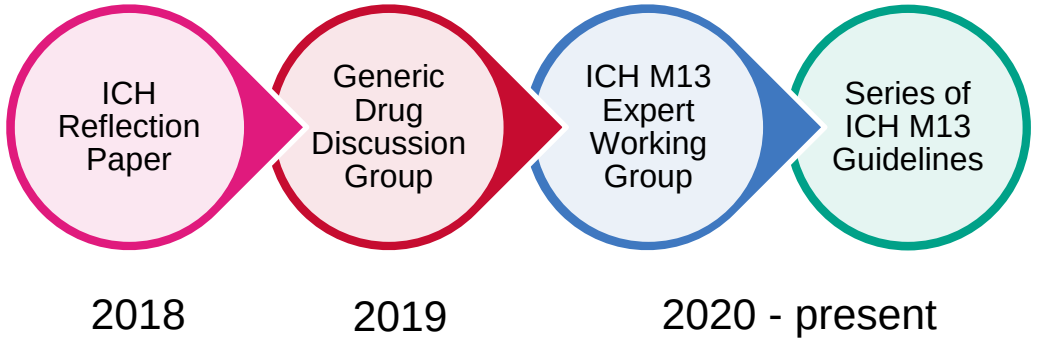
# ICH Reflection paper – Further opportunities for harmonisation of standards for generic drugs

- Reflection paper endorsed by the ICH Assembly on 13 November 2018
- Development and enhancement of ICH guidelines to support the harmonisation of scientific and technical standards for generic drugs
- ICH guidelines on standards for demonstrating equivalence for:
  - Non-complex dosage forms
  - Complex dosage forms
- International harmonisation for generics could lead to increasing patient access to pharmaceutical products globally
- Main topics across jurisdictions where alignment lacks are:
  - Requirements for test and reference products; stricter in US FDA than EU
  - Biowaivers; stricter in Japan's PMDA



# ICH M13A guideline (draft version)

Overview of comments received – 48 pages!




**BIOEQUIVALENCE FOR IMMEDIATE-RELEASE SOLID ORAL DOSAGE FORMS**
**M13A**

| Code | History | Date |
|---|---|---|
| M13A | Endorsement by the Members of the ICH Assembly under *Step 2* and release for public consultation. | 20 December 2022 |

**M13B**: waiver considerations for additional strengths

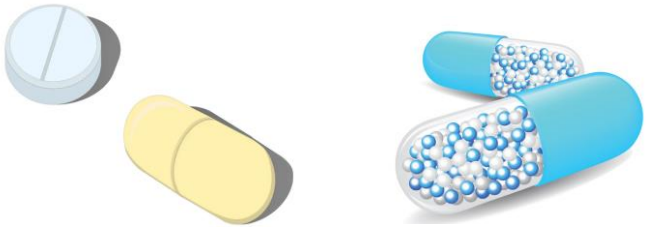
**M13C:** highly variable drugs, drugs with narrow TI, complex BE design and analysis

Currently open for public consultation

Estimate timepoint for adoption of the final guideline (step 4): June 2024

# ICH M13A - Objective

- Bioequivalence (BE) studies during both development and post-approval phases for orally administered immediate-release (IR) solid dosage forms designed to deliver the drug to systemic circulation
- The pharmacokinetic (PK) principles of the guideline are generally applicable to non-orally administered drug products with immediate action (e.g., rectal, inhalation and nasal drug products)
- Deviations from the guideline may be acceptable when justified
- Regulatory authorities should be conducted when an alternate approach is proposed or taken
- ICH M13A refers to ICH M9 guideline on biopharmaceutics classification System – based biowaivers and ICH E6 guideline on good clinical practice



# ICH M13A – Background


- **When are BE studies required?**

- Establish therapeutic equivalence for generic drug products to their respective comparator (reference) products **– Main focus**
- Bridge the formulation used in the clinical studies to the commercial formulation
- Support post-approval formulation and/or manufacturing process changes

- **When are two products considered bioequivalent?**

- Two products containing the same drug substance(s) are considered bioequivalent if their relative bioavailability (BA) (rate and extent of drug absorption) after administration in the same molar dose lies within acceptable predefined limits
- These limits are set to ensure comparable in vivo performance (i.e., similarity in terms of safety and efficacy)

Same drug substance?

Reference to the guideline on the investigation of BE?

# ICH M13A – Study population

## Healthy subjects

Adequate to detect formulation differences and allow extrapolation of the results to the intended population

## Patients

If the drug substance has adverse effects and the risks are unacceptable for healthy subjects, the study may be conducted in patients

# ICH M13A – Study population

- If a drug is intended for use in both sexes, it is recommended that the study includes male and female subjects

Sex Effect on Average Bioequivalence – Ibarra et al. (2017)

- Differences in gastrointestinal physiology between men and women can significantly affect the oral bioavailability discrimination of formulations
- Extrapolation of BE results from the male to the female population may not always be valid
- BE study should be performed with both male and female subjects in similar proportions

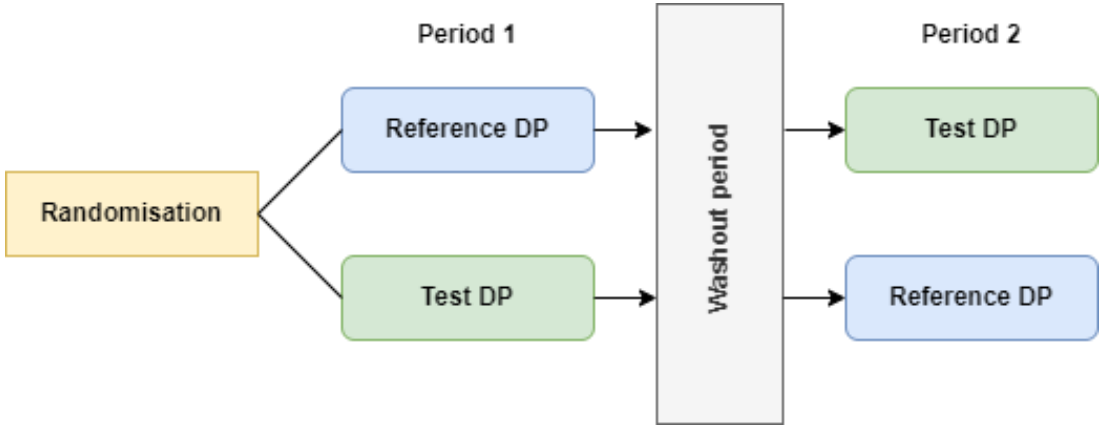
VS

Investigation on the existence of sex-by-formulation interaction in bioequivalence trials – Gonzalez-Rojano (2019)

- Upon assessment of 120 BE studies, there is no evidence to require BE demonstration in both sexes

# ICH M13A – Study design

- A randomised, single-dose, two-period, two-sequence crossover study design is recommended when comparing two formulations
- A multiple-dose study may be conducted in patients if a single-dose study cannot be conducted in either healthy subjects for safety/tolerability reasons or in patients for ethical reasons (steady state should be achieved)
- For drugs with long elimination half-lives, a parallel design may be employed when a crossover design is impractical due to need for a prolonged washout period

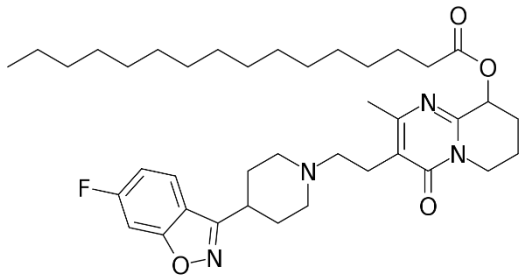



Single-dose studies provide the most sensitive conditions to detect differences in the rate and extent of absorption

# Example – Paliperidone palmitate

- Paliperidone palmitate depot suspension for injection 25 mg, 50 mg, 75 mg, 100 mg and 150 mg product-specific bioequivalence guidance

| | |
|---|---|
| **Bioequivalence study design****<br>*in case a BCS biowaiver is not feasible or applied* | **Single dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths), in healthy volunteers (if feasible) or in patients stabilized on other antipsychotic medication.<br>**Multiple dose:** any dose/strength (if the test product has the same concentration of active substance as the reference for all the strengths) in patients. |
| | **cross-over or parallel** |
| **Analyte** | ☐ **parent** ☒ **metabolite** ☐ **both**<br>**Background:** the prodrug, paliperidone palmitate, is not reliably measurable in plasma. Bioequivalence should be based on paliperidone. |
| | ☒ **plasma/serum** ☐ **blood** ☐ **urine** |
| **Bioequivalence assessment** | **Main pharmacokinetic variables:**<br>**Single dose:** $AUC_{0-t}$, $AUC_{inf}$, $C_{max}$ and $T_{max}$<br>**Multiple dose:** $AUC_{0-\tau}$, $C_{max,ss}$, $C_{\tau,ss}$ |
| | **90% confidence interval:** 80.00–125.00 % for $AUC_{0-t}$, $AUC_{inf}$, $C_{max}$, $AUC_{0-\tau}$, $C_{max,ss}$ and $C_{\tau,ss}$. Comparable median and range for $T_{max}$. |




Paliperidone palmitate is an atypical antipsychotic drug

Paliperidone is formed by ester hydrolysis

# ICH M13A – Sample size for BE studies

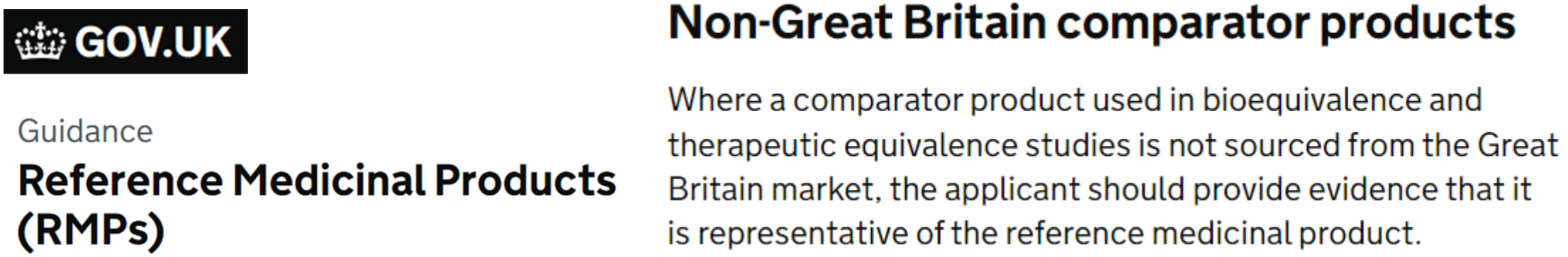
- The number of subjects to be included in the BE study should be based on an appropriate sample size calculation to achieve a pre-specified power and pre-specified type 1 error
- The use of ‘spare’ subjects is not acceptable
- The number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover design or 12 per treatment group for a parallel design

Clarification on the definition of ‘spare’ subjects required

Subjects who are treated but only included in the analysis if other subject withdraw (?)

# ICH M13A – Comparator and test products

- A comparator product is the drug product accepted by regulatory agencies that an applicant can use to compare against the test product in conducting a BE study
- The test product should usually originate from a batch at least 1/10 of production units or 100,000 units, whichever is greater, unless otherwise justified
- The assayed content of the batch used as a test product should not differ by more than 5% from that of the batch used as a comparator product
- BE studies with multiple comparator products or multiple test formulations

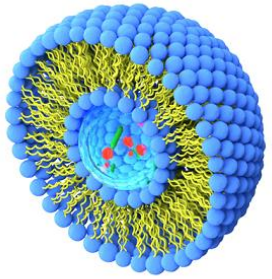


# ICH M13A – Fasting and fed conditions

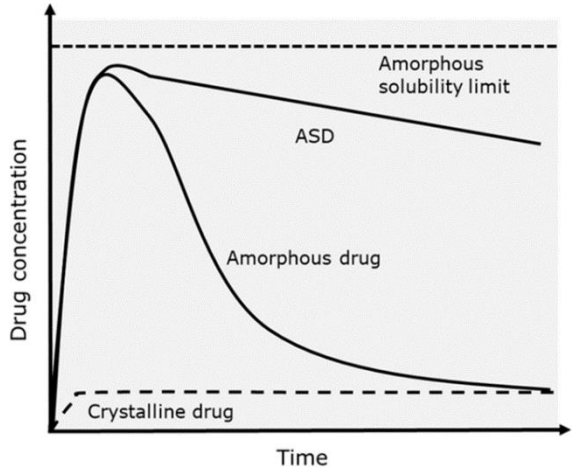
- Single-dose BE studies conducted under fasting conditions typically provide greater discrimination between the PK profiles of two products
- The design of a BE study regarding the use of fasting and/or fed conditions depends on the:
  - Dosing instruction of the comparator product
  - Drug substance and
  - Product formulation (‘non-high-risk’ and ‘high-risk’ products)
- The rationale for the selection of the type of BE studies (fasting vs fed or both) can be supported by modelling (e.g., qualified PBPK modelling/PBBM)

# ICH M13A – Non-high-risk *vs* High-risk products


- **Non-high-risk products**
  - BE under fasting or fed conditions
- **High-risk products (Risk of BE failure)**
  - Complex formulation design or manufacturing method leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal conditions between fasting and fed states
  - Solid dispersions, microemulsions, lipid-based formulations, nanoformulations
  - BE under both fasting and fed conditions



Liposomal formulation




'Spring and parachute' effect for amorphous solid dispersions

# ICH M13A – Non-high-risk *vs* High-risk products

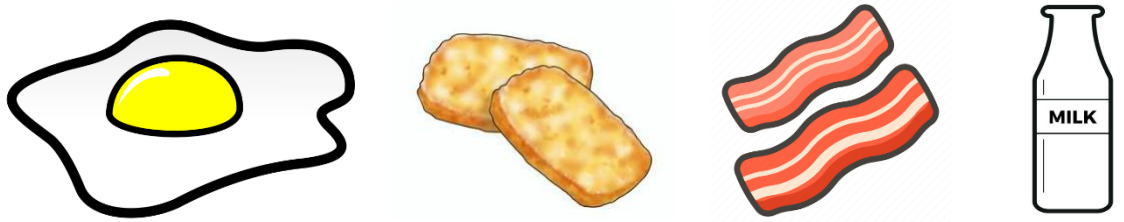
| Depending on the dosing instructions of the comparator product as well as the properties of the drug substance and product formulation | |
|---|---|
| Fasting BE only* | • Non-high-risk products<br>• Serious AEs are anticipated under fed conditions |
| Fasting and Fed BE | • High-risk products** |
| Fed BE only | • Non-high-risk products, labelled to be taken with food due to PK reasons<br>• Serious AEs are anticipated under fasting conditions |

* Fasting or fed BE: where the labelling indicates intake only with food due to tolerability reasons

** Irrespective of the product labelling with regards to food intake, apart from safety concerns

# ICH M13A – Standardisation with regards to meals and water

- The dose should be administered with a standardised amount of water, in the range of 150 to 250 ml
- For BE studies conducted under both fasting and fed conditions, the BE study under fed conditions should be conducted using a meal that has the potential to cause the greatest effect on GI physiology
  - High-fat and high-calorie meal
- For studies performed in patient populations who cannot tolerate the recommended meal composition, a pre-dose meal with a different caloric/fat content can be administered
  - Low-fat and low-calorie meal
  - Product-specific BE guideline of capecitabine film-coated tablets: ‘Fed state recommended to minimise the risk of vomiting, for example standardised light meal for patients participating in the BE study’

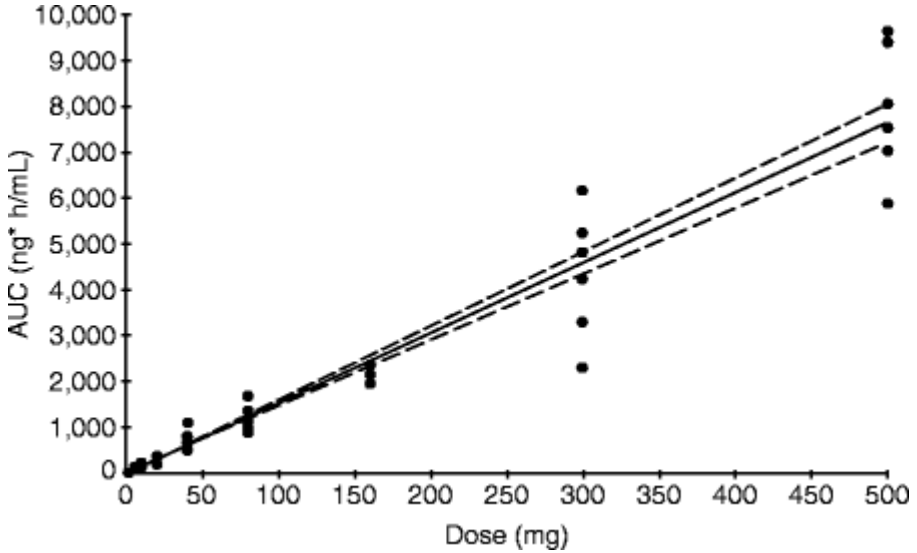


# ICH M13A - Dose or strength to be studied

- The strength to be used in the BE study depends on the dose proportionality in PK and solubility of the analyte.

Dose proportionality of both AUC and Cmax over the range of strengths ?

It may be addressed in M13B ?




Relationship of individual AUC values for X001 versus dose with linear regression (bold line) and the 95% confidence range (dashed line)

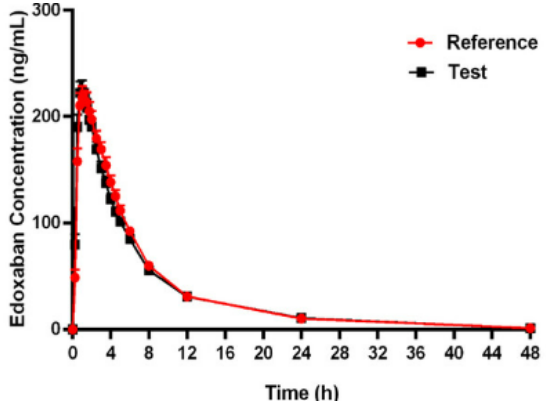
# ICH M13A – Enantiomers *vs* racemates

- The use of an achiral bioanalytical assay is generally acceptable
- A stereoselective assay measuring individual enantiomers in BE studies should be employed when it is known that all the following conditions have been met:
  - A) the enantiomers exhibit different PD properties
  - B) the enantiomers exhibit different PK properties
  - C) the exposure (AUC) ratio of enantiomers is modified by a difference in the rate of absorption
- It is sufficient to demonstrate BE for only the active enantiomer in cases where one enantiomer is inactive with respect to safety and efficacy

A stereoselective method should be used even if one of the following conditions is met

# ICH M13A - Sampling

- First point Cmax
  - Datasets where Cmax occurs at the first post-dose sampling time may result in exclusion of the data from affected subjects from the study
- Long Half-life drugs and truncated AUC considerations
  - AUC(0-72h) to be used in place of AUC(0-t)
- Early exposure
  - An additional PK parameter, such as AUC vs time curve between two specific timepoints (pAUC) may be applied




To exclude datasets where Cmax occurs in the first post-dose sampling time may be problematic

Subjects with first point Cmax are those with most rapid absorption, and so exclusion of these subjects may bias results towards conclusion of BE

# ICH M13A – Removal of data due to low exposure

- Data should only be removed from the statistical analysis based on protocol violations which are contemporaneously documented; prospective plan should be included in the study protocol
- An exception to the above can be made for a subject without measurable concentrations or only very low concentrations following either reference or test product administration
  - AUC for that period is less than 5% of the geometric mean AUC of the product in question, calculated without inclusion of data from the subject
  - Very low concentrations are considered the result of subject non-compliance; to be avoided by documenting mouth check of subjects
  - Exclusion of data for this reason to be accepted in exceptional cases (NMT one subject in each study)

Are low concentrations always the result of non-compliance?

Example: product-specific guideline of dasatinib

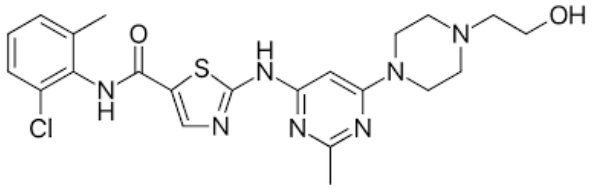
Need to widen the possibilities beyond just non-compliance

# Example - Dasatinib

- Dasatinib film-coated tablets 20, 50, 70, 80, 100 and 140 mg and suspension 10 mg/ml product-specific guidance
- Low-lier profiles in the fasted state observed both in test and reference; more likely a physiological effect

Requirements for bioequivalence demonstration (PKWP)*

| | |
|---|---|
| **BCS Classification** | **BCS Class:** ☐ **I** ☐ **III** ☒ **Neither of the two**<br>**Background:** dasatinib may be considered a low solubility compound. |
| **Bioequivalence study design**<br>*in case a BCS biowaiver is not feasible or applied* | **single dose**<br>**cross-over** |
| | **healthy volunteers** |
| | ☐ **fasting** ☐ **fed** ☒ **both** ☐ **either fasting or fed**<br>**Background:** Some subjects may randomly exhibit low concentrations of dasatanib when taking dasatinib products in the fasted state. Therefore, these products are considered with specific formulation characteristics and, consequently, bioequivalence should be evaluated under fasting and fed conditions. |




Dasatinib is a cancer growth blocker used to treat chronic myeloid leukaemia

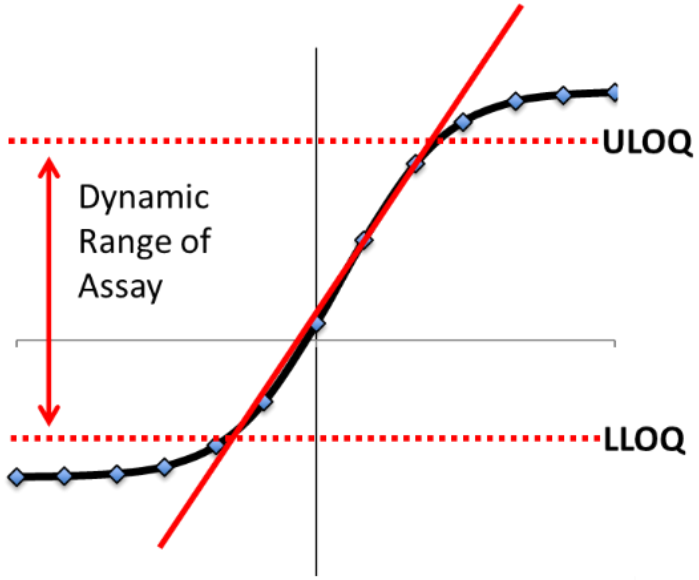
# ICH M13A – Potency differences in lots

- The results from the potency assay of the test and comparator products should be submitted and the test product batch should be within 5% of the comparator product batch
- In exceptional cases where a comparator product batch with a measured drug content within 5% of a test product batch cannot be obtained, a potency correction
- Reasons for justification of the potency correction include:
  - Potency data from multiple lots of comparator product, pending market availability
  - Consideration of the totality of evidence
- To be pre-specified in the study protocol
- Analyses to be provided for both the uncorrected data and for potency-corrected data
- If the potency correction is justifiable, the applicable BE standards should be met on potency-corrected data

Additional information given on potency correction compared to the guideline on investigation of BE

# ICH M13A – Carry-over and LLOQ

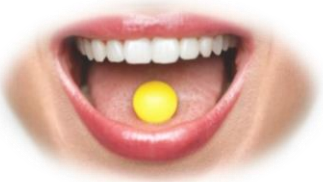
- If there are subjects for whom the pre-dose concentration is greater than 5% of the Cmax value for the subject in that period, then the pivotal statistical analysis should be performed excluding the data from that subject
- LLOQ should be less than the 5% of the Cmax




The statistical analysis should be performed excluding the data from that subject for that period

LLOQ should be less than 5% of the mean Cmax or of the lowest Cmax observed?

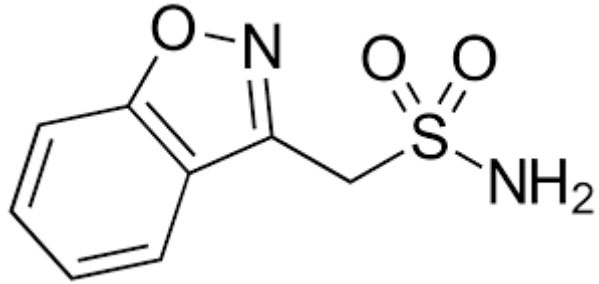
# ICH M13A – Orally disintegrating tablets



- Orally disintegrating tablets (ODTs) should be administered in BE studies according to the comparator product labelling with regards to intake of water
- If the comparator product labelling states that the ODT can be taken with or without water, the BE should be conducted without water (most discriminatory scenario)
- For new intended label use/instruction (e.g., ODTs as an extension to another orally administered IR product), the BE should be conducted according to the intended labelling
- If the new intended label use/instruction states that ODTs can be taken with or without water, a 3-arm BE study is recommended
  - Comparator IR oral dosage form as per labelling
  - ODT with water
  - ODT without water
- Similar handling is proposed for orodispersible films, buccal tablets, sublingual tablets and chewable tablets

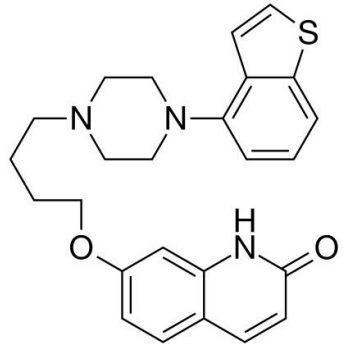
# Example – Zonisamide

- Zonisamide ODTs 25, 50, 100 and 300 mg product-specific bioequivalence guidance
- A fasting study using the 300 mg ODT strength
- Intake without water for the ODTs



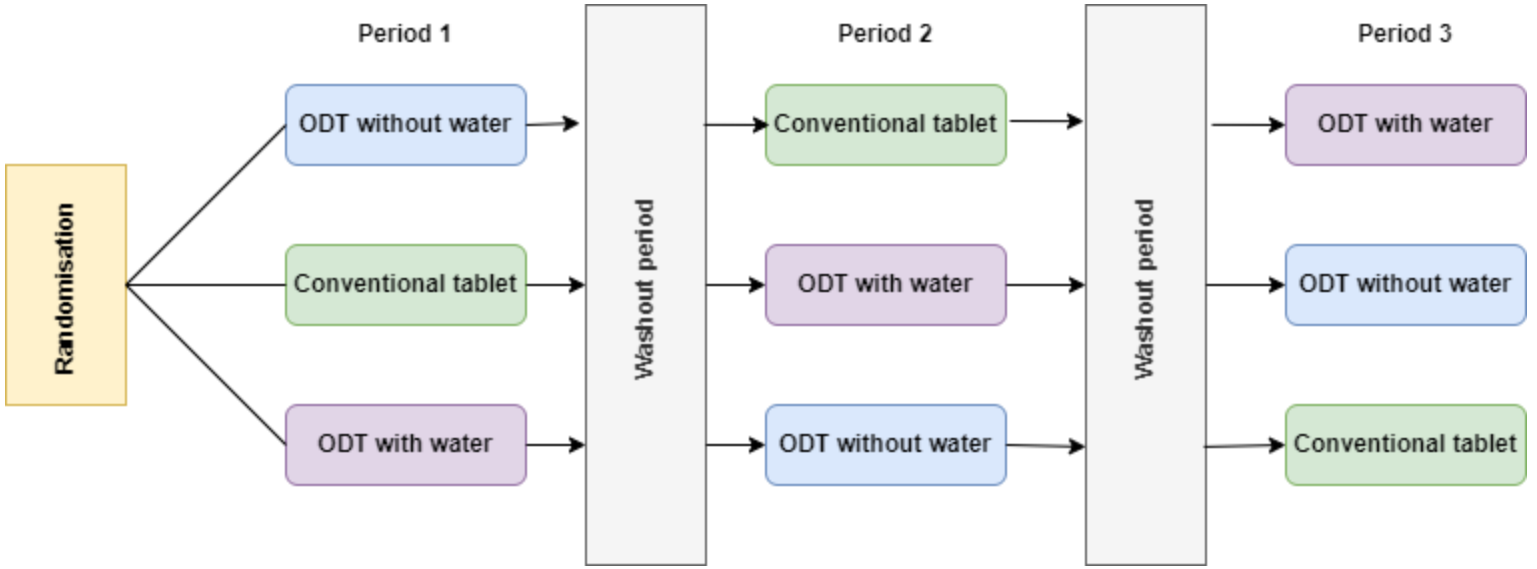

Zonisamide is a medication used to treat symptoms of epilepsy and Parkinson’s disease

# Example – Brexpiprazole ODTs 3-arm study



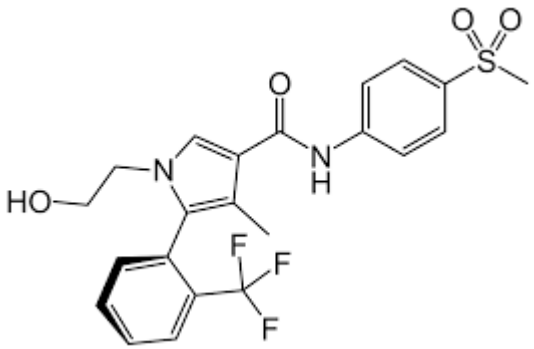

- BE study of brexpiprazole ODTs 2 mg
- Interventions:
  - Brexipiprazole ODT 2 mg with water
  - Brexipiprazole ODT 2 mg without water
  - Brexipiprazole conventional tablet 2 mg

Brexipiprazole is a medication used for the treatment of major depressive disorder and schizophrenia

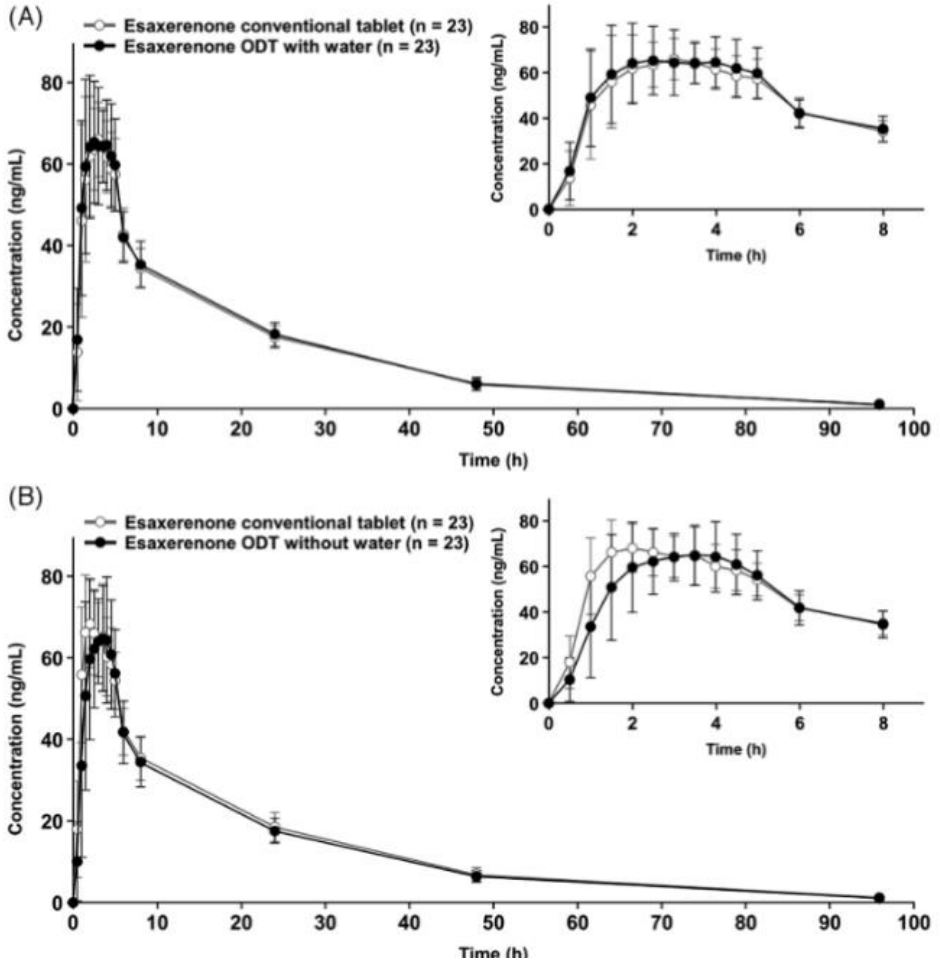


# Example – Esaxerenone ODTs two studies

- BE study of esaxerenone ODTs 5 mg
- Study 1
  - Esaxerenone 5 mg ODTs with water
  - Esaxerenone 5 mg conventional tablets with water
- Study 2
  - Esaxerenone 5 mg ODTs without water
  - Esaxerenone 5 mg conventional tablets with water




Esaxerenone is a nonsteroidal antimineralcorticoid



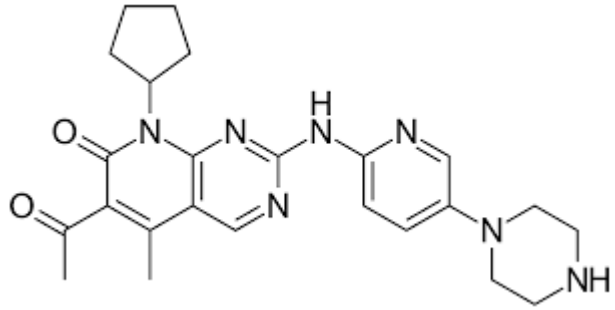
# ICH M13A – pH dependency

- The absorption of drug substances with pH-dependent solubility may be influence by the gastric pH
- When relative to the comparator product, there are qualitative or quantitative differences in the pH stabilising excipient(s), significant differences in manufacturing processes, or differences in salt form, BE under normal fasting conditions between the two products may not ensure BE of the two product in gastric pH-altered situation
- An additional BE study with concomitant treatment of a pH-modifying drug product would be generally be necessary to demonstrate BE
- A scientific justification could be provided to demonstrate that a BE study in a gastric pH-altered situation may not be needed
- Modelling such as PBPK, PBBM and virtual BE studies may be used to further assist the risk of bioinequivalence

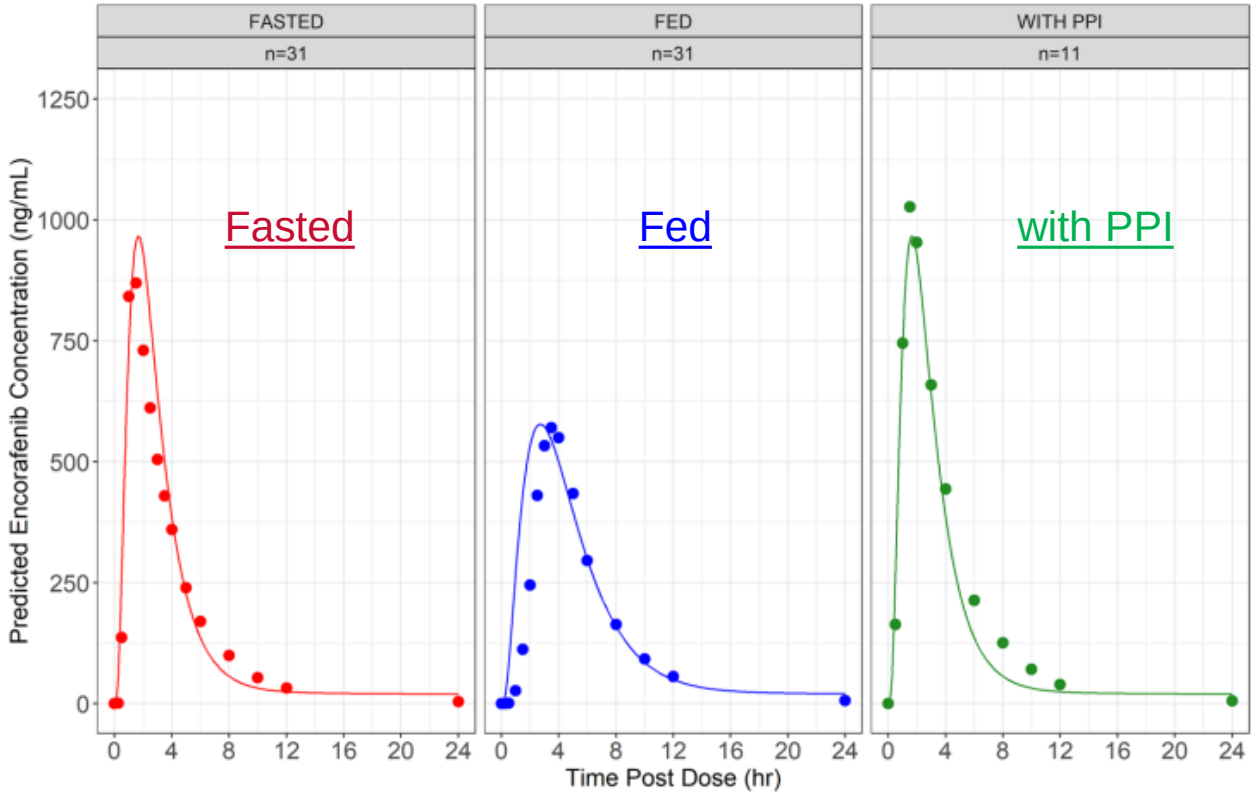
# Example – Palbociclib

- Palbociclib hard capsule 75 mg, 100 mg and 125 mg and film-coated tablet 75 mg, 100 mg and 125 mg product-specific bioequivalence guidance
- Capsules: one single-dose study under fed conditions
- Tablets: two single-dose studies under fasting conditions and under conditions of pre-treatment with proton pump inhibitor (PPI)
- In addition to the regular fasting conditions, a fasting study under conditions of multiple day pre-treatment with a PPI, such as pantoprazole (40 mg BID for 4 days), should be conducted.
- Solubility of palbociclib is pH dependent. PPIs may affect the bioavailability of Palbociclib under fasting conditions differently depending on the formulation

Palbociclib is used as a treatment for a certain type of metastatic breast cancer



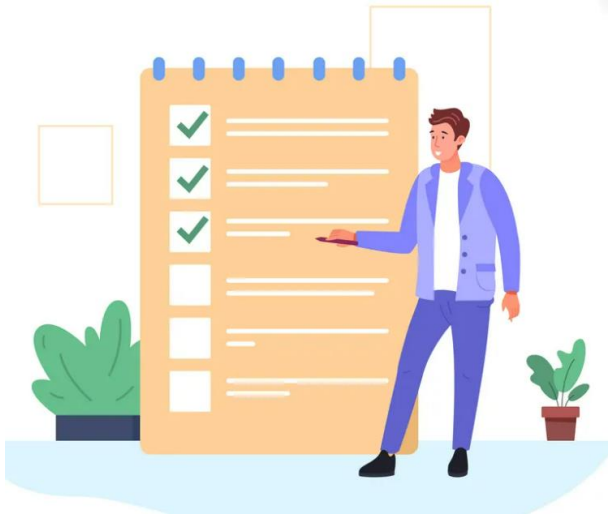
# ICH M13A – pH dependency




PBPK plasma predictions. Observed and simulated encorafenib exposures as a function of time following administration of a single 100 mg dose of encorafenib in fasted, fed and fasted with coadministration conditions

# Conclusions

- ICH M13A guideline is an important step towards promoting harmonisation of global drug development
- It is important to become clear if local guidelines will remain applicable
- Several comments have been raised that need to be addressed prior to the guideline becoming final
- The process of harmonisation will continue with ICH M13B and M13C guidelines



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