

Navigating the First ICH Generic Drug Draft Guideline “M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms”

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SBIA Webinar



Outline

- Objectives of the webinar
- Overview of ICH M13 guideline series
- Highlights of M13A draft guideline
 - Overview of content
 - Major differences between draft M13A and FDA's current draft ANDA BE guidance*
 - Additional discussion on selected topics
- Summary
- Panel discussion
- Audience Q & A

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ANDA: Abbreviated New Drug Application; BE: Bioequivalence

** Guidance for Industry: [Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application](#) (Aug 2021)*

Webinar Objectives



- Provide an overview of the draft M13A guidance
- Explain ICH Expert Working Group (EWG)'s current scientific thinking on selected topics
- Provide clarification on the FDA planning on the implementation of M13A for generic drug applications

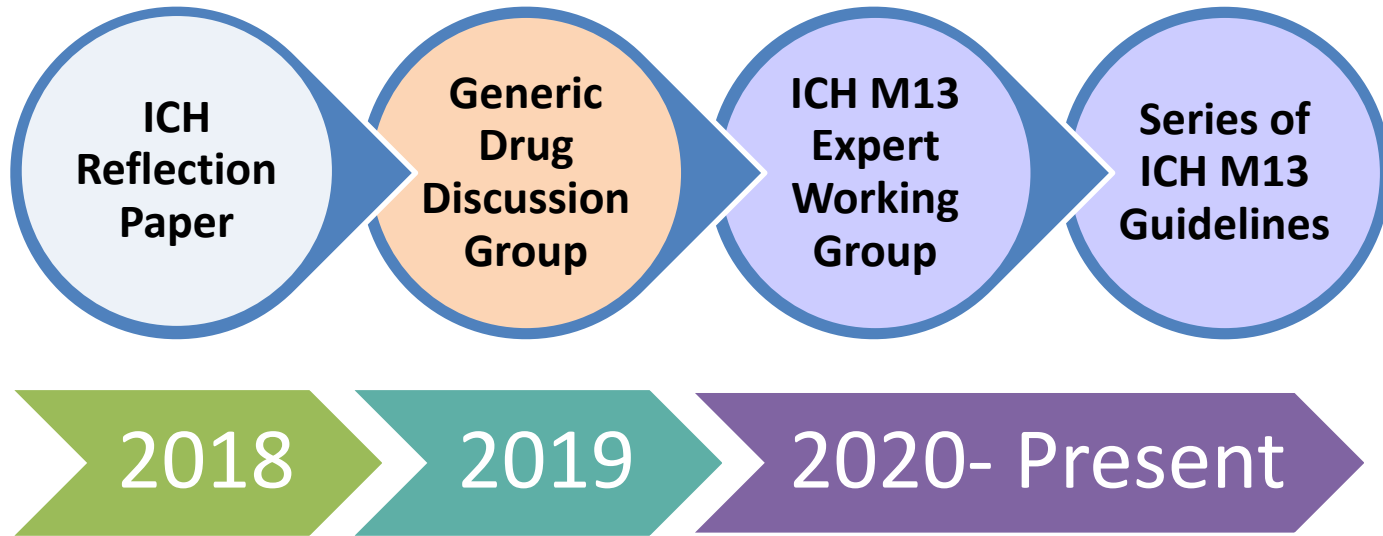
Although M13A covers both generic and new drugs, today's focus is on generic drugs.

Background (1)



- Generic drugs comprise a significant portion of the pharmaceutical market
- Bioequivalence (BE) assessment is important for establishing therapeutic equivalence for generic drug products to their respective comparator products
- ICH Reflection Paper on “*Further Opportunities for Harmonisation of Standards for Generic Drugs*” (endorsed by ICH in Nov 2018) outlines a strategic approach for developing and enhancing ICH guidelines to support the harmonization of scientific and technical standards for generic drugs
 - From non-complex to more complex products
- Common standards for global development for generics can improve access to generic medicines

Background (2)



M13: Bioequivalence for Immediate-Release Solid Oral Dosage Forms

M13 Objectives (1)



- Focus on **immediate-release (IR) solid oral dosage forms** designed to deliver drugs to the systemic circulation. For example,
 - Tablets
 - Capsules
 - Granules/powders for oral suspension
- Provide recommendations on conducting BE studies during:
 - Product development
 - Post-approval phases



M13 Objectives (2)

- Harmonize current regional guidelines/guidances
- Reduce need to conduct multiple BE studies for multiple jurisdictions
 - Reduce the need for multiple different sets of data and information from duplicative BE studies
- Support streamlined global drug development

Scope and Organization of M13 (1)



M13 guideline development includes three (3) tiers:

- **Tier 1 → M13A:** First guideline in the series
 - Scientific / technical aspects of study design and data analysis to support BE assessment
 - How regulatory decisions are made based on the BE assessment is out of scope
 - Acceptance of comparator products across regulatory jurisdictions
 - Could reduce burden of multiple clinical trials
 - Governed by local laws therefore out of scope

Scope and Organization of M13 (2)



- **Tier 2 → M13B:** Second guideline in the series
 - BE for additional strengths of a product line including biowaiver considerations
 - BE study(ies) conducted with one strength (bio-strength)
 - Relationship to bio-strength
 - Biowaiver from requirement for additional studies
 - Dose proportionality in the pharmacokinetics of the comparator product
 - Qualitative and quantitative composition comparison among strengths
 - Comparative in vitro dissolution
 - Assessment of similarity between dissolution profiles

Scope and Organization of M13 (3)



- **Tier 3 → M13C:** Third guideline in the series
 - BE study design, analysis, and assessment for
 - Highly variable drugs
 - Drugs with narrow therapeutic index (NTI)
 - Complex BE study design and analysis considerations

M13 Progress

M13A

- Start: Jul 2020
- Step 1: Dec 9, 2022
- Step 2: Dec 20, 2022
- **Current Status:** Step 3
Public Consultation

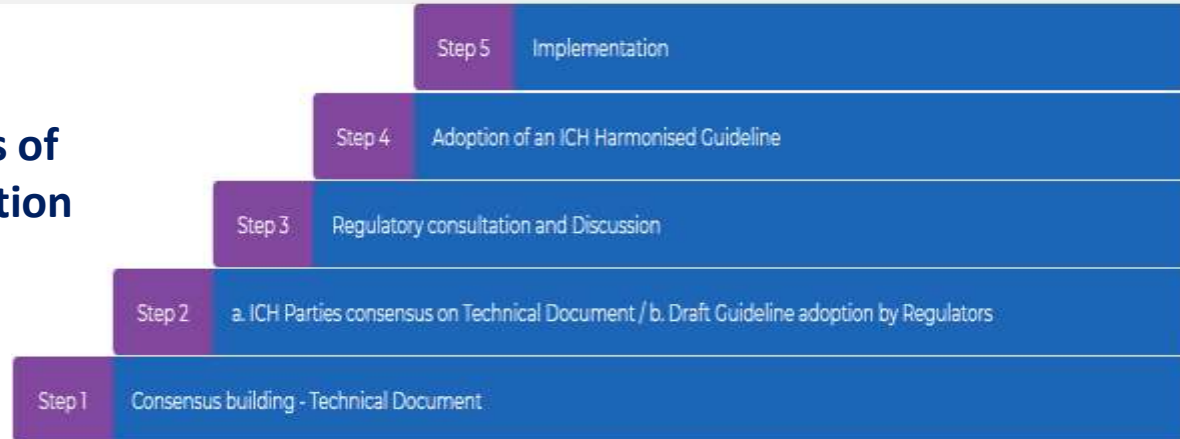
M13B

- Start: Nov 2022
- **Current Status:** Draft technical document under development towards consensus
- Step 1 (est.): Nov 2023

M13C

- Start: After M13B Step 2

ICH Process of Harmonization



Focus of This Webinar: M13A

- M13A: is the first guideline in the M13 series to harmonize the scientific and technical aspect of study design and data analysis to support BE assessment for orally administered **IR solid oral dosage forms**
 - The first ICH generic drug draft guideline developed following ICH reflection paper on “Further Opportunities for Harmonisation of Standards for Generic Drugs”
 - **Current Status: *Step 3* Public Consultation**

M13A Public Consultation Dates



- **ANVISA, Brazil** - Deadline for comments by 11 May 2023
- **EC, Europe** - Deadline for comments by 26 May 2023
- **FDA, United States** - Deadline for comments by 3 April 2023 [Docket No.: [FDA-2023-D-0093](#)]
- **HSA, Singapore** - Deadline for comments by 15 April 2023
- **Health Canada, Canada** - Deadline for comments by 25 May 2023
- **MFDS, Republic of Korea** - Deadline for comments by 7 April 2023
- **MHLW/PMDA, Japan** - Deadline for comments by 22 May 2023
- **NMPA, China** - Deadline for comments by 30 April 2023
- **Swissmedic, Switzerland** - Deadline for comments by 26 May 2023
- **TFDA, Chinese Taipei** - Deadline for comments by 30 April 2023

Table of Content of M13A Guideline (1)

- **1. Introduction**
 - 1.1 Objective
 - 1.2 Background
 - 1.3 Scope
- **2. General Principles in Establishing Bioequivalence**
 - 2.1 Study Design for Pharmacokinetic Endpoint Bioequivalence Studies
 - 2.2 Data Analysis for Non-Replicate Study Design

Table of Content of M13A Guideline (2)

- **3. Specific Topics**
 - 3.1 Endogenous Compounds
 - 3.2 Other Immediate-Release Dosage Forms
 - 3.3 Fixed Dose Combination
 - 3.4 pH-Dependency
- **4. Documentation**
- **5. Glossary**

M13A: Introduction (1)



- BE assessment is important for establishing therapeutic equivalence for generic drug products to their respective comparator products
- There may be situations in new (innovator) drug development when demonstration of BE may be critical for approval decisions
- BE studies are used by innovator and generic product developers for supporting post-approval formulation and/or manufacturing process changes
- The pharmacokinetic (PK) principles of this guideline are generally applicable to non-orally administered drug products with immediate action in which reliance on systemic exposure measures is suitable for establishing BE, e.g., certain rectal, inhalation, and nasal drug products
- Deviations from the recommendations in this guideline may be acceptable if appropriate scientific justification is provided
- Applicants are encouraged to consult the regulatory authority(ies) when an alternate approach is proposed or taken

M13A: Introduction (2)



ICH M9, Biopharmaceutics Classification System-Based Biowaivers: The Biopharmaceutics Classification System (BCS)-based biowaiver for oral IR

ICH E6, Good Clinical Practice: Principles and recommendation for conducting BE studies in human subjects

- **Out of scope:**
 - How regulatory decisions may be made based on BE assessment
 - Acceptance of comparator products across regions
 - BE for additional strengths of IR → M13B
 - BE for highly variable drugs and NTI drugs → M13C
 - PK study design or data analysis to support bioavailability (BA) assessment for new drug development in support of intended use or dosing recommendations in drug labelling, e.g., relative BA, food effect, drug-drug interactions, etc.

M13A: Study Design (1)

- Study Population
 - In general, healthy subjects
- Study Design
 - In general, a randomised, single-dose, two-period, two-sequence crossover study design
 - For safety/tolerability reasons, possibly multiple-dose study in patients
 - For drugs with a long elimination half-life: parallel design
- Sample Size

M13A: Study Design (2)



- Test Product
 - Representative of product to be marketed
- ★ • **Comparator Product**
 - Product accepted by regulatory authorities that can be compared against the Test Product in BE study
- ★ • BE studies with multiple comparator products or multiple test formulations

M13A: Study Design (3)



– Fasting and/or Fed Conditions



- Selection of the type of BE study(ies) (fasting or fed or both) and meal type(s) depends on
 - The dosing instructions of the comparator product
 - The properties of drug substance
 - The properties of the products being compared (“non-high risk” or “high risk”)

M13A: Study Design (4)

– Fasting and/or Fed Conditions



- **High-Risk Products (Risk of BE Failure)**
 - Products where the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal (GI) conditions between the fasting and fed states
- Different BE recommendations with regard to meals for “high-risk” and “non-high-risk” products

M13A: Study Design (5)



- Dose or Strength to be Studied
 - Dependent on the PK and solubility of the drug
 - In general, the highest strength should be administered if PK is dose-proportional
 - ★ – In case of more than dose proportional increase in PK: the highest strength
 - ★ – In case of less than dose proportional increase in PK:
 - If due to saturation of absorption: the lowest strength
 - If due to solubility or unknown reason: the lowest and highest strength

M13A: Study Design (6)

- Moieties to be Measured
 - Parent vs. metabolite
 - Enantiomers vs. racemates
- Sampling

Sufficient blood samples, including the pre-dose sample, should be taken to obtain a reliable estimation of the absorption phase, the T_{\max} and the extent of exposure, which is achieved when $AUC_{(0-t)}$ covers at least 80% of $AUC_{(0-\infty)}$

- First point C_{\max}
- Long half-life drugs
 - Truncated AUC
- Early exposure

M13A: Data Analysis (1)



- The following single-dose PK parameters should be tabulated:
 - ★ – Primary parameters: $AUC_{(0-t)}$ (or $AUC_{(0-72h)}$), C_{max} , and pAUC, where applicable
 - Additional parameters: $AUC_{(0-inf)}$, $AUC_{(0-t)}/AUC_{(0-inf)}$, T_{max} , k_{el} , $t_{1/2}$
 - $AUC_{(0-t)}$ should cover at least 80% of $AUC_{(0-inf)}$, except in case AUC is measured over 72 hours
- Standard statistical approaches should be employed
 - Non-replicate study
- Bioequivalence Criteria
 - For the primary PK parameters, the 90% confidence interval for the geometric mean ratio should lie within a range of 80.00 - 125.00%

M13A: Specific Topics (1)

- Endogenous compounds
- Other IR dosage forms
 - Orally Disintegrating Tablets (ODTs)
 - Chewable Tablets
 - Oral Suspensions
- Fixed Dose Combination (FDC) Products
 - BE should be demonstrated for all components (drugs) in the fixed-dose combination product according to the principles described in this guideline for non fixed dose products
- pH-Dependency



M13A: Documentation

- The report of the BE study should include the complete documentation of its protocol, conduct, and evaluation
- It should be written in accordance with ICH E3, *Structure and Content of Clinical Study Reports*
- Module 2.7.1 of the CTD should list all relevant BE studies conducted regardless of the study outcome. Full study reports should be provided for the BE study(ies) upon which the applicant relies for approval. For all other studies, synopses of the study reports (in accordance with ICH E3) are sufficient.

Summary of Major Differences in Recommendations Between Draft M13A and the Draft FDA ANDA BE Guidance (Aug 2021)*

* *Guidance for Industry: [Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application](#) (Aug 2021)*

Major Differences—1

Introduces the concept of high-risk and non-high-risk IR products and the recommendations for BE study design with regards to fasting and fed conditions and meal-types according to the risk category (Section 2.1.5)



High Risk and Non-High Risk Products

- **High Risk Products (Risk of BE Failure)**
 - For certain products, differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa
 - BE studies should be conducted under both fasting and fed conditions
- **Non-high Risk Products**
 - Results from a fasting BE study may be extrapolated to predict fed BE study outcome or vice versa
 - BE testing under only one condition, generally fasting, is sufficient

Fasting and Fed BE



Current FDA Draft ANDA BE Guidance:

Recommends Both Fasting and Fed BE Studies for All Oral IR Drug Products

Fasting BE Studies Only	<ul style="list-style-type: none"> 1) Products should be taken on an empty stomach (per the labeling) 2) Serious adverse events are anticipated under fed conditions
Fed BE Studies Only	<ul style="list-style-type: none"> 1) Serious adverse events are anticipated under fasting conditions

Draft ICH M13A:

Depending on the dosing instructions of the comparator product as well as the properties of the drug substance and product formulation

Fasting BE only*	<ul style="list-style-type: none"> 1) Non-high-risk products 2) Serious adverse events are anticipated under fed conditions
Fasting and Fed BE	High-risk products**
Fed BE only	<ul style="list-style-type: none"> 1) Non-high-risk products, labeled to be taken with food due to PK reasons 2) Serious adverse events are anticipated under fasting conditions

* Fasting or fed BE: where the labeling indicates intake only under fed conditions, due to tolerability reasons

** Irrespective of the product labelling with regard to food intake, except for safety concerns

High-Risk Products

(Risk of BE Failure)



Includes drug products containing low solubility drug substances that are formulated using,

- specialized technologies and/or manufacturing methods to optimise the food effect or enhance the solubility and dissolution. E.g.,
 - microemulsions
 - amorphous solid dispersions
 - lipid-based formulations
 - nanotechnology
- substantially different manufacturing technology or particle size control method for the test and comparator products
or
- have excipient differences that are likely to impact dissolution, solubility, or permeability of the test and comparator products differently

Meal Type for Fed BE Study



- **High-Risk Products**
 - Fed BE: irrespective of the product labelling with regard to food intake
 - The meal should be a high-fat and high-calorie meal*
- **Non-High-Risk Products**
 - Fed BE: e.g., where the labelling indicates intake only under fed conditions, due to a PK reason
 - Either a high-fat, high-calorie meal or a low-fat, low-calorie meal, may be administered
 - Labeling specified meal

** For BE studies in patients, a different fat/calorie content meal may be used as appropriate for the patient population.*

Fasting and Fed BE (Cont'd)

- Rationale should be provided for the selection of BE study(ies) (fasting or fed or both) and meal type based on the understanding of the comparator product and the test product (high or non-high risk)
- Same recommendations with regard to fasting and fed study conditions, apply when BE studies are deemed necessary to bridge formulation and/or manufacturing process changes during pre- or post-marketing phases

Major Differences—2



Expands the study design and statistical analysis of BE studies to support testing of either multiple comparator products from different regions or multiple test products with different formulations in the same trial (Section 2.2.5)



Comparator Product

- In the context of M13A, a comparator product is the drug product accepted by regulatory agencies for use in conducting a BE study
- Expansion of the recommendation on the study design for accepting multiple comparator products from different regions in one trial is intended to streamline the BE demonstration

Testing Multiple Comparator Products



- A single higher-order crossover BE study with multiple comparator products against the same test product
 - No alpha adjustment is needed
 - BE decisions will be made independently for a single comparator within a single jurisdiction
- Preferable for the statistical analysis to only test two at a time (pairwise comparison)
- Study results from all comparisons performed should be included in the clinical study report

Testing Multiple Test Formulations



- A single higher-order crossover BE study with different formulations of the test product against the same comparator product
- Alpha adjustment depends on the underlying objectives of the trial
 - If the objective is to achieve BE for all test formulations versus the comparator product, then no alpha adjustment is needed
 - If the objective is to show BE for any of the test formulations, then multiplicity adjustment may be needed
- The objective of the trial and method for multiplicity correction should be pre-specified in the study protocol

Major Difference—3

Introduces a new section on ‘pH-Dependency’ related to drug substances with pH-dependent solubility to recommend an additional BE study in certain cases (Section 3.4)

pH-Dependency (1)



- Absorption of drug substances with pH-dependent solubility may be influenced by the gastric pH
- BE under normal fasting conditions between the two products may not ensure BE of the two products in a gastric pH-altered situation
 - Differences in pH stabilizing excipients, salt-form or manufacturing process between formulations, may result in a different BE outcome in a gastric pH-altered situation

pH-Dependency (2)



- An additional BE study with concomitant treatment of a pH-modifying drug product (e.g., PPIs) would generally be necessary for drugs showing pH-dependent solubility/dissolution
 - Recommendations for study design and data analysis not specified in M13A
 - Future Q&A: examples of a study design, drug names, comparative dissolution, PBPK modeling, etc.
 - Lack of sufficient knowledge/experience in this topic area
 - Product-specific guidances: e.g., palbociclib tablets (NDA 212436)
- Can justify not conducting an in vivo BE study by assessing the BE risk, based on totality of evidence

Major Differences—4

Clarifies exceptional cases, where removal of data due to low exposure may be accepted (Section 2.2.1.1)

Removal of Data Due to Low Exposure

- Data should only be removed from the statistical analysis based on protocol violations which are contemporaneously documented
 - in general with no more than 1 subject in each study
- A subject is considered to have very low concentrations if the AUC for that period is less than 5% of the geometric mean AUC of the product in question
 - may result from subject non-compliance and bring the reliability of dose administration into question
- All subject data should be submitted and potential extreme values flagged with appropriate documentation as part of the application

Major Differences—5

Introduces exceptional cases where potency correction may be accepted with proper justification (Section 2.2.2.3)

Potency Correction

- The measured potency of the comparator batch should be within 5% of the test batch used in the BE study
- In exceptional cases potency correction may be accepted with supporting justification
 - e.g., potency data from multiple lots of comparator product, pending market availability, considering the totality of evidence
- If potency correction is to be used, it should be pre-specified in the study protocol
- If the potency correction is justifiable, the applicable BE standards should be met on potency-corrected data
- Analysis should be provided for both uncorrected data and for potency-corrected data

Additional Discussion on Selected Topics

- Study population
- Parent vs metabolite
- Early exposure
- Dose or strength to be studied
- Other IR dosage forms: ODTs, chewable tablets and oral suspension

Study Population



	Current FDA Draft ANDA BE Guidance	Draft ICH M13A
Subjects	Healthy subjects or <u>general population</u>	Healthy subjects
Intended for use in both sexes	<u>Similar proportions</u> of males and females or provide a <u>justification</u> of using a single-sex population	Recommend to include male and female subjects
Genotype and/or phenotype		May consider for safety or PK reasons
Other	<p><u>Geriatric</u>: If a drug product is predominantly intended for use in the elderly, include many subjects at or above age 60 or provide a justification</p> <p><u>Pediatric</u>: If a drug product is predominantly intended for use in pediatric patients younger than 6 years, justify that BE study results in adults are relevant to the pediatric population (including how the inactive ingredients are appropriate for use)</p>	<u>BMI</u> : Prefer a BMI of 18.5 and 30.0 kg/m ²

Parent versus Metabolite



Current FDA Draft ANDA BE Guidance

-Measure primary metabolite(s), formed directly from the parent compound, if they are formed substantially through presystemic metabolism (gut wall or gut lumen metabolism) and contribute significantly to the safety and/or efficacy of the product

-Analyze the parent drug measured in these BE studies using a CI approach

-Use the metabolite data to provide supportive evidence of a comparable therapeutic outcome

-If the parent drug concentrations are too low to allow reliable analytical measurement, the metabolite data obtained from these studies should be subject to the CI approach for BE demonstration.

Draft ICH M13A

-In some rare cases, demonstration of BE based on both parent drug and primary active metabolite where formation of the metabolite could be influenced by formulation differences

-e.g., drugs that have metabolites formed through gut wall or gut lumen metabolism that contribute to efficacy or safety

-For some prodrugs, acceptable to demonstrate BE based on a primary metabolite (a first-step metabolite of the parent drug) without measurement of the parent if the parent drug levels are too low to allow reliable bioanalytical measurement

Sampling: Early Exposure



Current FDA Draft ANDA BE Guidance	Draft ICH M13A
<ul style="list-style-type: none">-T_{max} can also provide important information regarding the rate of absorption-Evaluate T_{max} differences for any clinical implications	<ul style="list-style-type: none">-In some situations where C_{max} and AUC_t may not be sufficient to adequately assess the BE when the early onset of action is clinically relevant, an additional PK parameter, such as pAUC, may be applied
<ul style="list-style-type: none">-Use a pAUC as an exposure measure if specified in the applicable PSG-Beginning and ending times for the pAUC should relate to a clinically relevant measure	<ul style="list-style-type: none">-Use of pAUC in case an early onset of action is clinically relevant <p>pAUC is typically evaluated from the time of drug administration until a predetermined time-point that is related to a clinically relevant PD measure</p>

Dose or Strength to be Studied

Current FDA Draft ANDA BE Guidance

- Highest strength
- Acceptable to use a lower strength for safety reasons if linear elimination has been documented over the therapeutic dose range
- In other cases (such as non-linear elimination), applicants may contact FDA via a controlled correspondence if there is no applicable PSG or if the proposed strength differs from what is recommended in the applicable PSG

Draft ICH M13A

- Depends on the dose proportionality in PK and solubility of the analyte
- Acceptable to use a lower strength for safety and/or tolerability reasons and dose proportional PK (AUC and C_{max}) has been documented over the range of strengths
- Assessment of dose proportionality should be based on a single-dose study
- In general, the highest strength should be administered if PK is dose-proportional
- In case of more than dose proportional increase in PK: the highest strength
- In case of less than dose proportional increase in PK:
 - If due to saturation of absorption: the lowest strength
 - If due to solubility or unknown reason: the lowest and highest strength

Other IR Dosage Forms



	Current FDA Draft ANDA BE Guidance	Draft ICH M13A
ODTs	-With or w/o water per labeling → BE studies without water	-Same as FDA's if with or w/o water for BE studies -If w/o, wet mouth w small amount of water, no intake of fluid for 1 hr
Chewable Tablets	-Must chew before swallowing per labeling → BE studies of chewed -Option of chew or swallow in whole per labeling → BE studies of whole with 240 mL water	-No mention of swallow in whole -Similar to ODTs with respect to water intake
Oral Suspension	Generally same as other solid oral dosage forms	
Orodispersible films, buccal tablets or films, sublingual tablets	Sublingual tablets – should not swallow, place under the tongue until dissolved	Similar to ODTs



Implementation of M13A

- FDA planning on the implementation of M13A for generic drug applications
 - Existing drug development plan in accordance with currently published product-specific guidances (PSGs) or recommendations from the agency
 - New development plan



Summary

- The harmonized M13A guideline provides recommendations on:
 - BE study design
 - Principles for conducting BE studies
 - BE standards for IR solid oral dosage forms
- This harmonized guideline will reduce the need for additional in vivo BE studies and supports streamlined global drug development
- Comments received on draft M13A will be considered by the M13 EWG while finalizing the M13A
- The process of harmonization will continue with M13B and M13C

Challenge Question 1

- What is the most significant difference between recommendations in M13A as compared to FDA's current draft ANDA BE guidance?
 - A. Recommendations for fasting vs. fed BE study
 - B. BE for long half-life drugs
 - C. Multiple comparator products
 - D. Batch size for pivotal studies

Challenge Question 2

- Which of the following products are not covered in M13A?
 - A. Immediate release oral product
 - B. Modified release oral product
 - C. Orally disintegrated tablets
 - D. Chewable tablets
 - E. Granules/powders for oral suspension

Resources

- [FDA Draft Guidance: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms \(January 2023\)](#)
- [ICH M13A Step 2 Presentation \(January 2023\)](#)
- [FDA Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application \(August 2021\)](#)
- [FDA Draft Guidance: Statistical Approaches to Establishing Bioequivalence \(December 2022\)](#)
- [FDA Office of Generic Drugs Global Generic Drug Affairs](#)
- [Product-Specific Guidances for Generic Drug Development \(main page\)](#)