M13A: Bioequivalence for Immediate-Release Solid Oral Dosage Forms – Implementing the Final Guidance

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November 21, 2024
SBIA Webinar

Learning Objectives

- Provide an overview of the final guidance and main changes from the draft guidance
- Provide clarifications and explain scientific thinking on main topics in M13A and the Q&A document
- Discuss FDA's implementation of M13A for generic drug applications including product-specific guidance revisions

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

Outline

- Presentations
  - Overview of ICH M13 guideline series
  - Highlights of M13A final guidance and main changes from draft guidance
  - Clarifications and explanations of the scientific thinking on main topics in M13A and the Q&A document
  - FDA's implementation of M13A for generic drug applications including FDA's revisions on product-specific guidances (PSGs)
- Panel discussion
- Audience Q & A
- Closing remarks

ICH: The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; ANDA: Abbreviated New Drug Application; BE: Bioequivalence; Q&A: Questions and Answers

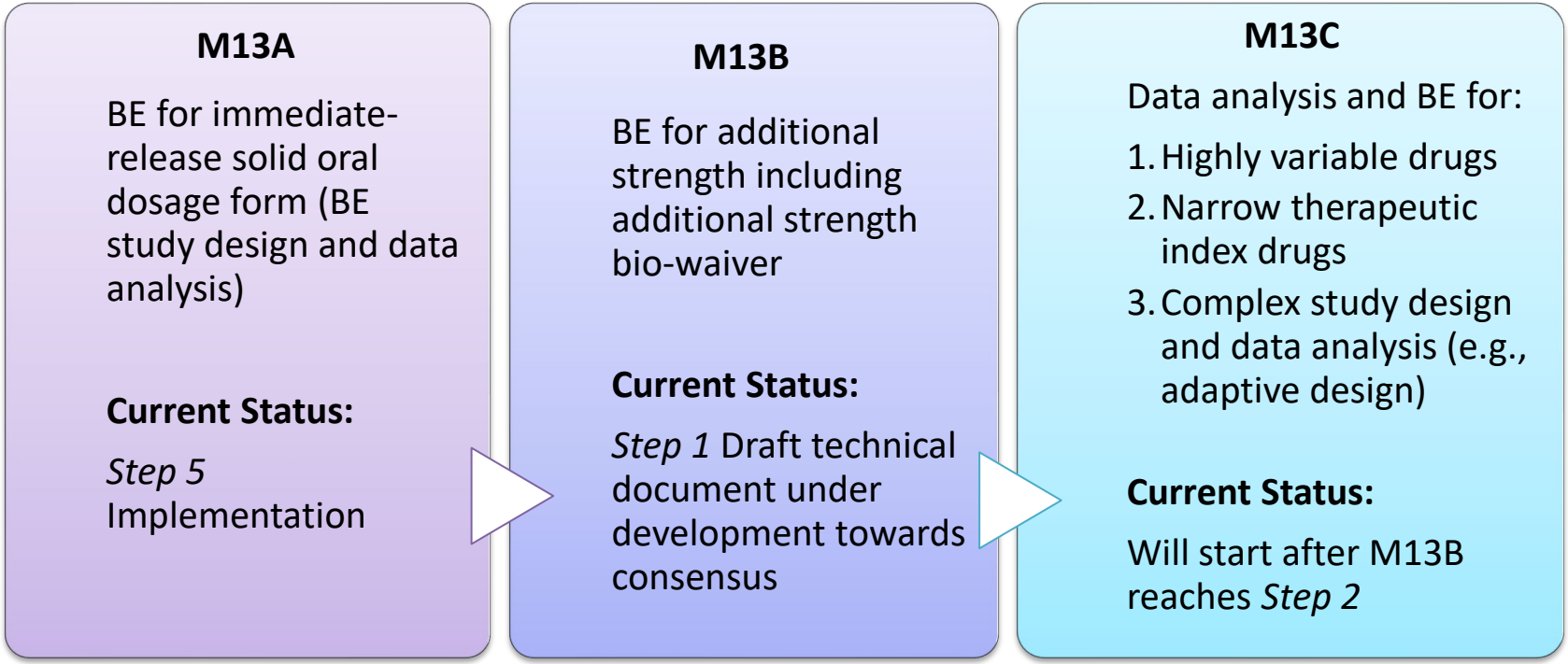
Bioequivalence Assessment

Bioequivalence (BE) assessment is important for establishing therapeutic equivalence for generic drug products to their respective reference listed drugs (“comparator” products)

- BE ensures that generic drugs demonstrate comparable pharmacokinetic properties to their brand-name counterparts
- 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

*__Comparator__ is defined in M13A as “an investigational or marketed product, i.e., active control, or placebo, used as a reference in a clinical trial. In the context of this guideline, 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."

M13 Guideline Series



BE: Bioequivalence

https://www.ich.org/page/multidisciplinary-guidelines#13-0

M13 Guideline Series and Timeline

M13A

- Start: Jul 2020
- *Step 1*: Dec 9, 2022
- *Step 2*: Dec 20, 2022
- Step 4: July 23, 2024
- **Current Status:** *Step 5;* Ready for regulatory implementation

M13B

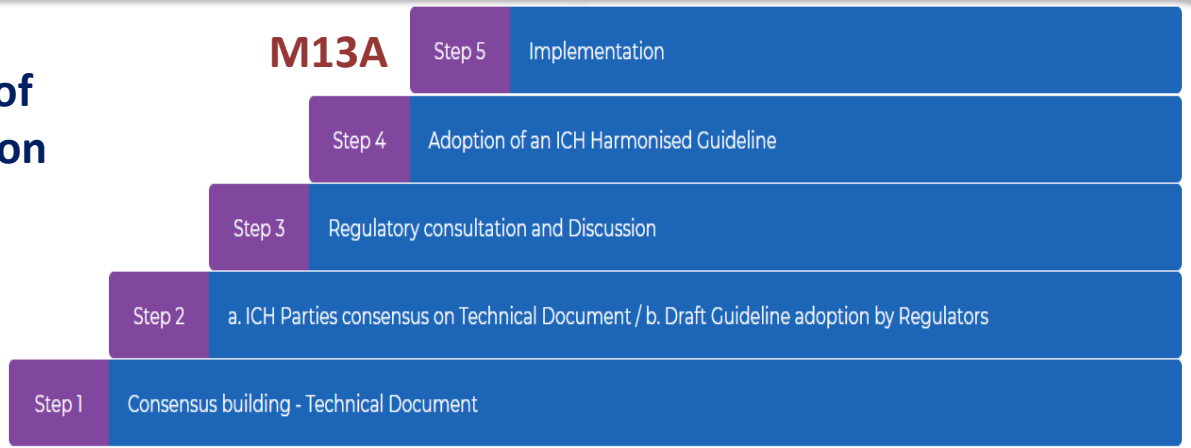
- Start: Nov 2022
- **Current Status:** *Step 1;* Draft technical document under development towards consensus
- *Step 2 (est.)*: Feb 2025

M13C

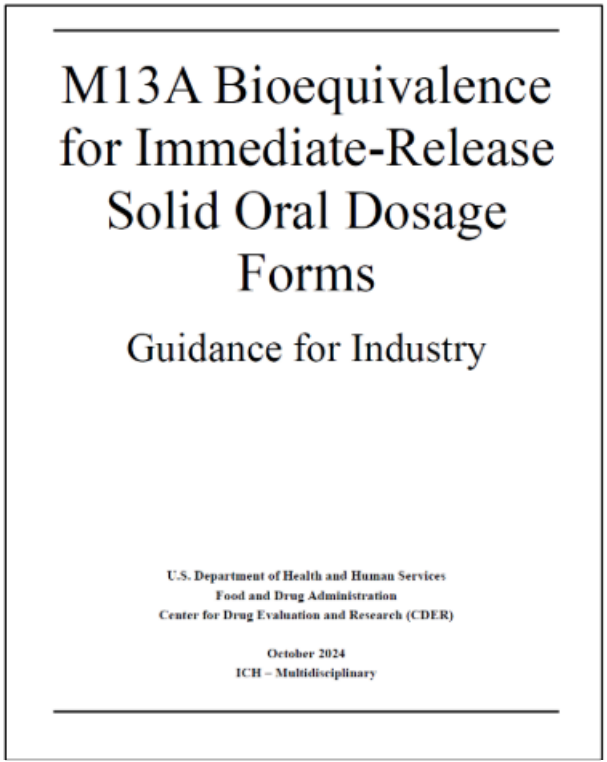
- Start: After M13B reaches *Step 2*

ICH Process of Harmonization

www.ich.org



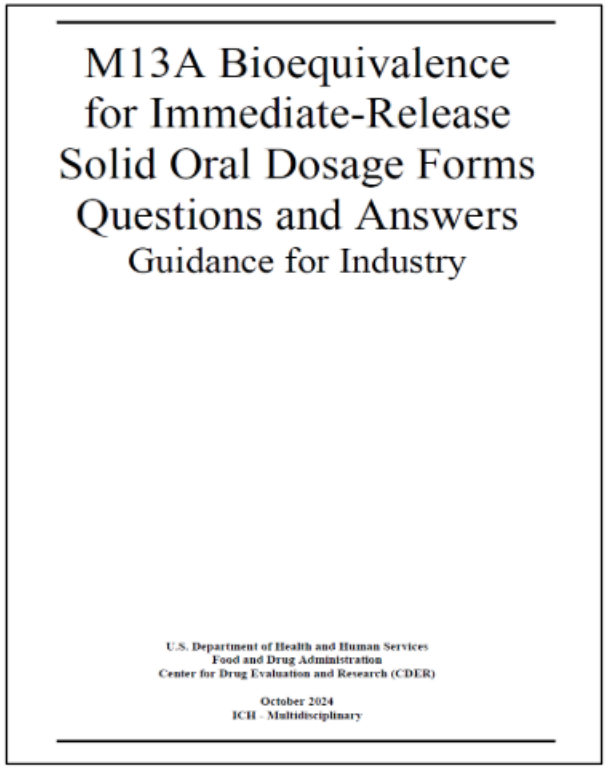
FDA Published M13A Final Guidance and its Q&A (Oct 2024)


M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2024
ICH – Multidisciplinary


M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms Questions and Answers

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

October 2024
ICH – Multidisciplinary

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms

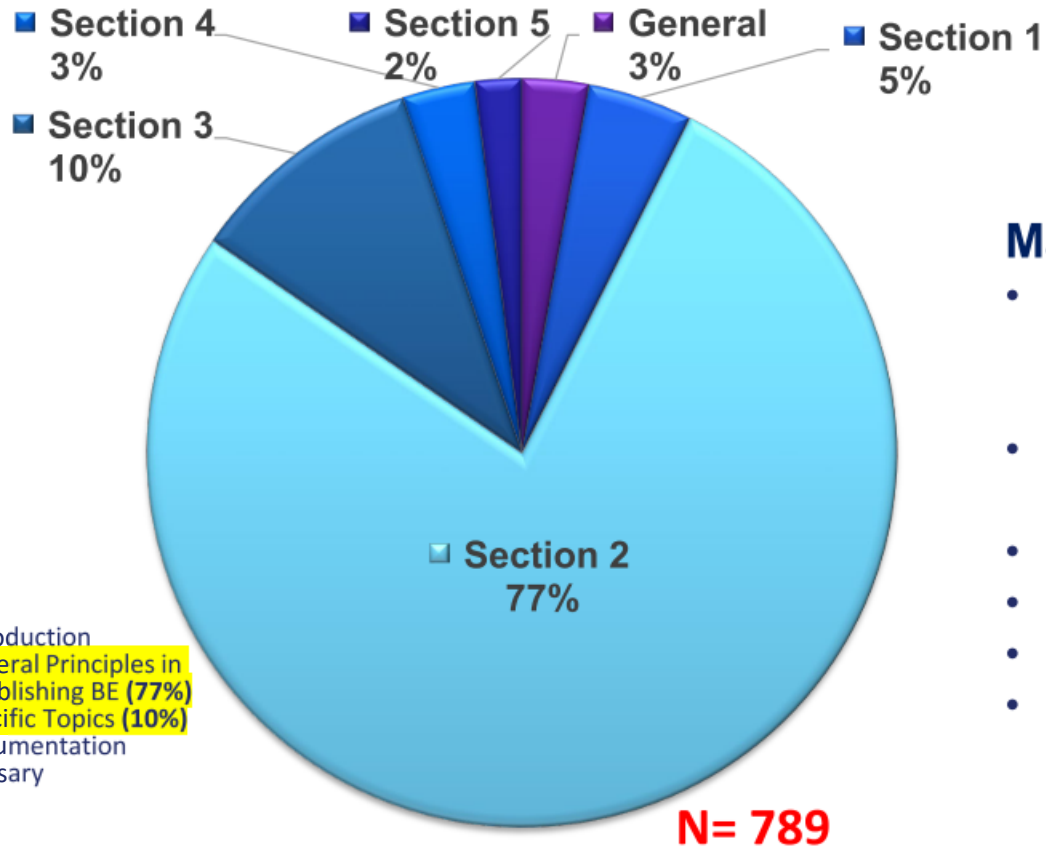
Table of Contents of M13A Final Guidance (1)

Table of Contents of M13A Final Guidance (2)

- **III. Specific Topics (3)**
  - A. Endogenous Compounds (3.1)
  - B. Other Immediate-Release Dosage Forms (3.2)
  - C. Fixed Dose Combination (3.3)
  - D. pH-Dependency (3.4)
- **IV. Documentation (4)**
- **Glossary (5)**

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m13a-bioequivalence-immediate-release-solid-oral-dosage-forms

Comments Received



1. Introduction
2. General Principles in Establishing BE **(77%)**
3. Specific Topics **(10%)**
4. Documentation
5. Glossary

N= 789

Main Comment Themes

- Clarification on “high-risk” and when fed BE study is needed
- Dose proportionality assessment
- Study population
- Data analysis
- Group effect
- Alignment of study design with product labeling

Main Changes Made from the Draft Guidance

- Modifications have been made based on comments received
- Mainly to provide clarification, e.g.,
  - "High-risk" products
    - "…drug products with special characteristics that result in a higher risk of **bioinequivalence** due to food effects…"
  - Data analysis
  - PK dose proportionality assessment
  - Early exposure
  - pH-dependency

Additional Resources Provided

- "Questions and Answers" document
  - To provide further clarity and to assist implementation
    - Section 2: 11 Q&A
    - Section 3: 7 Q&A
    - Section 4: 1 Q&A
- Step 4 Presentation

FDA Q and A guidance (Oct 2024) (ICH M13A Questions and Answers (July 2024))
ICH M13A Step 4 Presentation (July 2024)

Before M13A (Prior to Harmonization)

- Different regulatory agencies have different recommendations for BE study designs and criteria to support generic drug approval
  - For immediate-release (IR) oral products
    - FDA generally recommended both fasting and fed BE studies
    - Several other regulatory agencies including European Medicines Agency (EMA), generally recommended a BE study under fasting conditions only
- Differences in general BE guidances had led to different PSG recommendations
  - Multiple BE studies to meet recommendations from multiple jurisdictions

M13A: A Risk-Based Approach to Determine BE Study Conditions with Regard to Meals

- **High-Risk Products (Risk of Bioinequivalence)**
  - 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 (Q&A 2.4 and Q&A 2.5)
- **Non-High-Risk Products**
  - A single BE study is sufficient to ensure there is no clinically significant difference in BE under different meal conditions
  - BE testing under only one condition which is most sensitive, generally fasting, is sufficient

Significant Impact of M13A on ANDA Submissions to the U.S. Fasting and Fed BE

Prior to M13A:

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

Fasting BE Studies Only	1) Products shou… stomach (per th… 2) Serious adver… fed conditions
Fed BE Studies Only	1) Serious adverse events are anticipated under fasting conditions

M13A:

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

	…sk products …erse events are anticipated under fed
	…ucts**
Fed BE only	…sk products, labeled to be taken with food due to PK reasons 2) Serious adverse events are anticipated under fasting conditions

Estimated savings of 50 million dollars per year based on numbers of ANDAs FDA received (200 ANDA approvals in FY2024 for products impacted by these BE recommendation changes)

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

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

FDA Draft Guidance: Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (August 2021)

M13A Final Guidance (Oct 2024)

FDA's Proactive Measures to Facilitate Implementation

- Organized trainings for external and internal stakeholders
  - SBIA webinar in May 2023 (M13A draft guidance)
  - FDA internal training and awareness
- Strategized the process to delineate non-high-risk drugs from high-risk drugs for PSG revision
  - Prioritized to provide immediate benefit (removing one BE study)
- Initiated revision to the draft general ANDA BE guidance (Aug 2021) to align with M13A
- Continued research projects on specific topics to build knowledge

FDA's Implementation and Alignment Efforts (1)

- FDA published final M13A guidance in Oct 2024 following ICH adoption of final M13A guideline in July 2024
- FDA revised >800 oral IR product PSGs to align with M13A
  - 814 revised PSGs posted in Oct 2024
  - Primary focus - Assess risk evaluation for "High-Risk" and "Non-High-Risk" oral IR drug products
  - The most significant change to PSGs (i.e., two BE studies to one BE study)
  - Reduce the need for additional in vivo BE studies compared to what FDA recommended prior to M13A
  - Support streamlined global drug development

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

FDA's Implementation and Alignment Efforts (2)

- Of more than 1,150 published PSGs of oral IR drug products, ~160 PSGs were excluded from the FDA's initial efforts for PSG revision to align with M13A, if they are
  - Narrow therapeutic index drugs
  - Locally acting drug products
  - Products with PSGs recommending BE studies in patients
  - Products with PSGs recommending only one BE study
- ~150 PSGs of oral IR drug products considered as "High-Risk" products were not revised
  - Continue to recommend two BE studies
  - Solid dispersions; lipid-based formulations (e.g., self-emulsifying drug delivery system); nanotechnologies (e.g., micro/nano-emulsions); gastro-retentive formulation; polymer-based (e.g., functional coating); critical excipients
- This initial revision efforts to align with M13A revised ~72% of FDA's existing PSGs for oral IR products and ~37% of total number of FDA published PSGs

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

FDA's M13A Implementation for Generic Drug Applications:

PSG Revisions to Align with M13A

- Points to consider for delineating the risk-categories of drug products (high-risk vs. non-high-risk)
- Clarifications and explanations of the scientific thinking on selected topics in M13A and the Q&A document

Fed or Fasting BE Studies PSG Revision

- FDA's initial set of PSG revisions focused on PSGs for oral IR products that recommended both fed and fasting BE studies in healthy subjects
- Evaluation of risk categories
  - High-risk: No revision, continue to recommend two BE studies
  - Non-high-risk: Two BE studies → one BE studies
    - Either under fasting or fed conditions
      - Product characteristics and RLD labeling

Evaluation of Risk Categories "High-Risk" and "Non-High-Risk" Products

Factors considered include:

- Biopharmaceutic properties of the drug substance
  - BCS class, BCS solubility subclass (weak acid, weak base), permeability or fraction absorbed
- Complexity of the formulation design or manufacturing technology/process of the products
  - Many IR formulations are conventional (simple, non-complex)
  - High risk design identified included lipid filled capsules, solid dispersions, emulsion formers
  - Pseudo MR formulations with release controlling polymers

MR: modified release

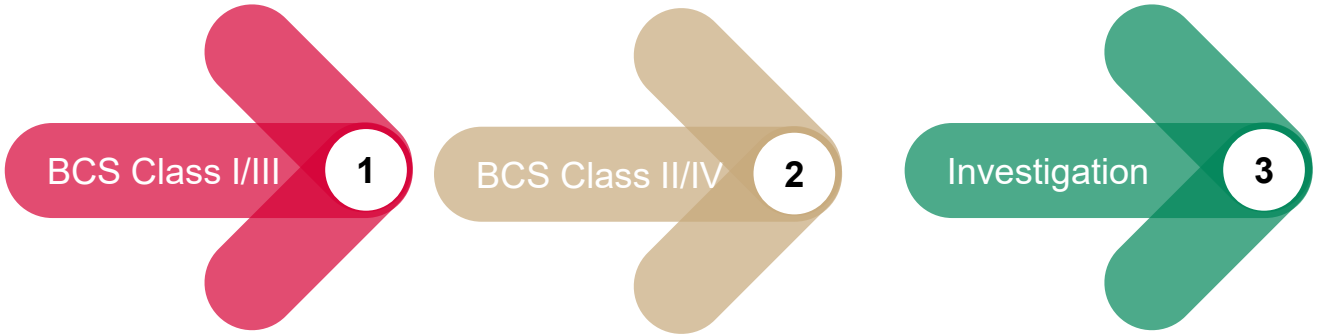
Evaluation of Risk Categories "High-Risk" and "Non-High-Risk" Products

Factors considered include (Cont'ed):

- Excipients **that are likely to impact disintegration, dissolution, solubility, or permeability of the test and comparator products differently, e.g.,**
  - pH modifiers at levels high enough to impact GI environment
    - And a single BE study is not sufficient to manage this risk
  - Surfactants may not always be considered high risk
    - The fasting study is may be more sensitive to evaluate the effectiveness of solubilization, in some cases
- Dosing instructions with regards to food intake in the RLD (comparator) labeling
- Clinical risk and size of the food effect

RLD: reference listed drug

Risk-Based Evaluation for Study Types



Tier 1:
- BCS I and III drugs
- Critical excipients
- Formulation design

Tier 2:
- Solubility
- Permeability
- Dissolution
- Food Effect

Tier 3:
- NDA product variants
- NDA different solid dosage forms
- ANDAs cross-study

Slide courtesy: Qi Zhang, Ph.D.

Fed or Fasting BE Studies PSG Revision

- Over 800 PSG were revised
- PSGs represent FDA's evaluation of the risk categorization of the RLD
- If a generic applicant adds formulation risk factors not found in the RLD, e.g., uses a solid dispersion formulation
  - FDA may ask for more information, e.g.,
    - Biorelevant dissolution data
    - PBPK modeling
    - A fed BE study

PBPK: physiologically based pharmacokinetic

M13A: High-Risk Products

M13A Recommendation:

- **BE studies under both fasting and fed conditions are necessary for high-risk products, irrespective of the drug product labeling with regard to food intake, if safety permits**
  - Testing across the range of GI conditions is necessary to minimize the risk of bio-inequivalence for these products
    - PK performance of low solubility drug substances enhanced via complex formulation and/or manufacturing technologies may be sensitive to varying GI conditions
    - Differences in the process, or excipients used to produce solid dispersion could result in a different interaction with the GI conditions
    - Fasting or fed condition alone is not sensitive to assess the impact of these potential differences
- **A high-fat, high-calorie meal is recommended for the fed BE study**
  - Allows to test under greatest perturbation of GI conditions

Role of RLD Labeling: "Take on an Empty Stomach" High-Risk Products

- **Currently Posted PSGs:** One fasting BE study

- **PSG Revision**: No plan to revise the PSGs to add a fed BE study unless there is a clinical concern or the labeling is changed
  - FDA identified <5 currently posted PSGs for high-risk products that are labeled to be taken on "an empty stomach"
  - FDA will consider M13A when developing new PSGs

Role of RLD Labeling: Silent or "Take without Regard to Food" or "Take with Food" High-Risk Products

- **Currently Posted PSGs:** Two BE studies (fasting and fed)

- **PSG Revision:** None

Meal types:

- In general, PSGs do not specify FDA's standardized meal (high-fat, high-calorie) for fed BE studies

- For BE in patients, FDA will continue to accept a different fat/calorie content meal

M13A: Non-High-Risk Products

M13A Recommendation:

- **A single BE study (either fasting or fed) is recommended for non-high-risk products**
- **Either a high-fat, high-calorie meal or low-fat, low-calorie meal is acceptable for the fed BE study**

Rationale: The PK performance of these products is not expected to be impacted under varying GI conditions

Role of RLD Labeling: "Take on an Empty Stomach" Non-High-Risk Products

A single fasting BE study is recommended for non-high-risk products when the drug is labeled to be taken only under fasting conditions

- **Previously Posted PSGs:** One BE studies (fasting)
- **PSG Revision:** None

Role of RLD Labeling: Silent or "Take without Regard to Food" Non-High-Risk Products

A single fasting BE study is recommended for non-high-risk products

PK performance of these products is not expected to be impacted under varying GI conditions

Fasting BE study is recommended when the drug is labeled to be taken without regard to meal

- the state of administration (fasting or fed) is not expected to influence the PK comparability of the products
- fasting state is preferred over the fed state (more sensitive, greater power to discriminate between PK profiles)

- **Previously Posted PSGs:** Two BE studies (fasting and fed)
- **PSG Revision:** Yes, removed fed BE study

Role of RLD Labeling: "Take with Food" Non-High-Risk Products (1)

A single fed BE study either with a high-fat, high-calorie meal or a low-fat, low-calorie meal if labeled to be taken with food due to PK reason

Variability in the spectrum of GI conditions is not expected to significantly influence the performance of these products

- it is not necessary to test under extreme perturbation of GI condition (e.g., using a high-fat, high-calorie meal), but it is also not precluded
- testing under less severe GI perturbation (e.g., using a low-fat, low-calorie meal) is also acceptable
  - may better reflect the type of meals a patient is likely to consume
  - no single meal type can represent the diverse range of meals patients may consume

Role of RLD Labeling: "Take with Food" Non-High-Risk Products (2)

FDA's recommendation for a high fat, high-calorie meal* does not reflect the same flexibility which M13A provides

For non-high-risk products to be taken with food for PK reasons

- FDA will consider the recommendation of alternate meal types in M13A for new PSGs and ANDA assessments (with adequate justification)

- **Previously Posted PSGs:** Two BE studies (fasting and fed)
- **PSG Revision:** Yes, removed fasting BE study

** For BE studies in patients, FDA accepts a different fat/calorie content meal*

Role of RLD Labeling: "Take with Food" Non-High-Risk Products (3)

A single fasting or fed BE study is acceptable if labeled to be taken with food due to tolerability reasons or other non-PK reasons

- Fasting BE study is recommended if a non-high-risk drug is labeled to be taken with food, for tolerability reasons
  - Dosing with food is recommended primarily for a non-PK reason
  - Tolerability from chronic use may not be of concern for single use, e.g., if the GI irritation is minor from a single use
- FDA applied some judgement to the PSG

  ~10 PSGs are for products labeled to be taken with food but recommend a fasting BE study, fasting can be more sensitive for various reasons
- **Previously Posted PSGs:** Two BE studies (fasting and fed)
- **PSG Revision:** Yes, removed fed BE study

Drugs with pH-Dependent Solubility (1)

M13A Recommendation: For a drug with pH-dependent solubility and expected to be taken with an acid-reducing agent e.g., a proton pump inhibitor (PPI), an additional study with concomitant administration of a PPI may be needed to address the risk of bioinequivalence, if

- The comparator product is designed explicitly to overcome the effect of altered gastric pH by addition of pH modifying excipient(s) and the test product either does not use or uses qualitative or quantitative different pH modifier(s)
  - Besides pH modifying excipients, differences in salt or polymorphic form, or significant differences in manufacturing process between formulations may also affect the pH-dependent solubility of the Test product and RS differently

- The impact of a sustained increase in gastric pH on the drug bioavailability can be underestimated from fasting or fed BE study

Drugs with pH-Dependent Solubility (2)

PSG Revision: FDA's initial efforts do not cover these PSGs

- In recent years, FDA has been recommending an additional study with PPI in the PSGs, as needed, e.g., Palbociclib Tablets
- For new PSGs, FDA will consider the recommendations in M13A

Alternative Approaches to PSGs and M13A

Both FDA and M13A offer flexibility to use alternate approaches, e.g.,

- Comparative disintegration and dissolution in biorelevant media, modeling such as PBPK modeling and simulation

Prospective applicants should,

- Provide appropriate scientific justification if an alternative approach is proposed
  - e.g., proposal to conduct only one BE study for “high-risk” products

- Provide rationale for selection of the study design with regard to the study type and meal
  - Intended to trigger applicants to have a thorough understanding of the potential for a formulation-dependent food-effect for their products

RS: reference standard

Commonly Asked Questions (1)

Q: We conducted BE studies under both fasting and fed conditions on submission batches, but PSG recommends only fed study. Please advise if we should submit only the fed study per the PSG, or both fasting (pass or fail) and fed studies?

Q: For the existing non-complex product, if the fed study failed, and the revised PSG no longer recommends a fed study to demonstrate BE, can the industry submit passing fasting study only?

A: FDA regulations (21 CFR parts 314 and 320) require the submission of data from **all** BE studies the applicant conducts on the same* drug product formulation as submitted for approval

- includes pilot studies and pivotal failed studies, in addition to pivotal passing studies

M13A (Documentation Section IV)

- Recommends to submit all relevant BE studies conducted, regardless of the study outcome

* Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (May 2011)

Commonly Asked Questions (2)

Q: If the fed BE study is removed in the revised PSG, should a complete report of the fed BE study be provided in the original ANDA or would only the summary of the fed BE study provided in Module 2.7 tables be sufficient?

A: A complete report needs to be submitted for the BE studies upon which the applicant relies for approval

For each additional study conducted on the same drug product formulation (such as the fed BE study, in this case), either a complete or summary report* should be submitted (BE Summary Tables in Module 2.7)

If FDA believes there may be BE issues or concerns with the drug product—FDA may request for a complete report

* Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs (May 2011); Guidance for Industry: Good ANDA Submission Practices (2022)

Commonly Asked Questions (3)

Q: If the PSG recommends only a fasting BE study and our application was submitted with both fasting and fed BE studies, how will FDA treat my additional fed study for the purpose of drug approval?

A: FDA reviews data from all studies in the application, especially those conducted on the same drug product formulation.

The fed study may receive an abbreviated review.

Most likely FDA will not ask applicants to repeat the study that is not recommended in the PSG, unless evaluation of the data raises potential concerns about the performance of the product.

FDA's M13A Implementation for Generic Drug Applications:

Focus on PSG Revisions
(Additional M13A and Other Revisions)

PSG Revisions to Align with M13A

FDA PSG Forecast

- Significant change – Two BE studies → one BE study
  - Remove the BE recommendations for BE studies under either fasting or fed conditions
- In Sept 2024, FDA posted a list of PSGs with the Planned Revision Category with Description
  - Minor Revision: remove recommendations on fasting or fed BE study to align with ICH M13A
- In Oct 2024, 814 PSGs were revised, the forecast website was updated with Modifications from the Planned Revisions in the PSGs on some published PSGs
  - If the planned revision was to remove a fasting (or fed) BE study, actual posting recommended to remove a fed (or fasting) BE study instead
  - Continue to recommend both fasting and fed BE studies
- Additional 10 PSGs will be revised with planned publication dates of November 2024 and February 2025 with regular PSG batch posting

Upcoming Product-Specific Guidances for Generic Drug Product Development | FDA;
BCS: Biopharmaceutics Classification System

Other PSG Revisions

FDA PSG Forecast Posting

- In Sept 2024, FDA posted a list of PSGs with the Planned Revision Category with Description
  - Minor Revision: remove recommendations on fasting or fed BE study to align with ICH M13A
  - Minor Revision: add a BCS-based biowaiver option
  - Editorial Revision: revisions to language and formatting as appropriate

- In Oct 2024, 814 PSGs were revised, the forecast website was updated with Modifications from the Planned Revisions in the PSGs on some published PSGs
  - Other Minor Revision – added BCS Class I or III-based biowaiver option
  - If the planned revision was to remove a fasting (or fed) BE study, actual posting recommended to remove a fed (or fasting) BE study instead
  - Continue to recommend both fasting and fed BE studies

Upcoming Product-Specific Guidances for Generic Drug Product Development | FDA;
BCS: Biopharmaceutics Classification System

FDA PSG Posting for Generic Drug Products

Active Ingredient(s)	Route of Administration	Dosage Form	RLD or RS Application Number	Planned Revision Category with Description	Product Complexity	Planned Publication	Modifications from the Planned Revisions in the PSGs Published on Oct 30, 2024
Amitriptyline Hydrochloride	Oral	Tablet	012703	Minor Revision: Remove recommendations on fed BE study to align with ICH M13A	Non-Complex	Published 10/2024	Additional Minor revision: Added BCS Class I-based biowaiver option
Amoxicillin; Clavulanate Potassium	Oral	For Suspension	050575	Minor Revision: Remove recommendations on fasting BE study to align with ICH M13A	Non-Complex	Published 10/2024	Minor Revision: Remove recommendations on fed BE study to align with ICH M13A

Minor Revision – PSG Revisions to Align with M13A

- For PSGs of Non-High-Risk Products
  - Remove recommendations on fasting or fed BE study to align with ICH M13A – Minor Revision category
    - *Minor Revision - any revision to a PSG that is not considered critical or major, including but not limited to when a PSG is to be revised to add an in vivo or in vitro BE option, to clarify recommended study design, to certain study(ies), to provide alternative (less burdensome) approaches to the currently recommended study(ies), to add information on newly approved strengths of the RLD, or to make other recommendations that would not generally result in additional recommended BE study(ies) or evidence by an ANDA applicant necessary to support FDA approval. Minor revisions include both in vivo and in vitro changes.*

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development; RLD: reference listed drug

Minor Revision – PSG Revisions to Align with M13A

Revision to **chewable tablet and ODT PSGs** – administration of a drug with or without water

	M13A	Previously Posted PSGs	Updated PSGs
ODTs	With regard to intake of water, administer according to the comparator product labeling; If ODT can be taken with or without water, administer without water in a BE study	Water may be taken after 5 mins and use of "liquid" is mentioned	Without water and deleted "liquid"
Chewable Tablets	Same as ODTs	Silent with respect to how to administer the chewable tablets with respect to water or chewing	Chew then swallow without water

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021479.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_050597.pdf;
ODT: orally disintegrating tablet

PSGs to Align with M13A: Study Subjects

- Recommend “Healthy subjects”
  - remove “General Population”, “Normal”, “Healthy, General Population”
- Consider the risks to female subjects of reproductive potential
- Should not include pregnant or lactating female subjects
- Recommend male contraception if a drug has embryo-fetal toxicity and pose transferability issues to female partners of reproductive potential
- Recommend “Healthy males not of reproductive potential or healthy females not of reproductive potential”

Minor Revision – Other PSG Revisions Study Subjects

- Recommend a single-sex study population if drugs are intended for use in a single-sex
  - e.g., oral contraceptives for the prevention of pregnancy; progestin for the treatment of secondary amenorrhea, endometriosis and abnormal uterine bleeding
    - Revised to “Healthy non-pregnant, non-lactating females” from “Healthy males and non-pregnant females, general population”

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021098.pdf

Study Subjects in BE studies

	ICH M13A	Previously posted PSGs	Updated PSGs
	Healthy subjects	"General population", "normal", "healthy, general population"	Healthy subjects (healthy males and non-pregnant, non-lactating females
Intended for Use in Both Sexes	Consider the inclusion of male and female subjects	Continue to recommend both sexes	Continue to recommend both sexes
Intended for Use in a Single-Sex	Silent	Healthy males and non-pregnant females, general population	Healthy males; Healthy non-pregnant, non-lactating females
Specific Risk to Females of Reproductive Potential	Consider the risk to females of reproductive potential; should not include pregnant or lactating females	Some missing pregnant or lactating info	Healthy females not of reproductive potential; Healthy non-pregnant and non-lactating females
Male Contraception	Recommend male contraception if a drug has embryo-fetal toxicity and pose transferability issues to female partners of reproductive potential	Often silent	Healthy males not of reproductive potential; Recommend male contraception

Minor Revision – Other PSG Revisions

- For PSGs of Non-High-Risk Products
  - Other Minor Revisions made to the PSGs
    - Add a BCS-based biowaiver option
    - Add recommendation of a reference scaled BE approach for drugs that are highly variable
    - Remove or add Risk Evaluation and Mitigation Strategies (REMS)

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development

Minor Revision – Other PSG Revisions

- Added BCS Class I/III-based biowaiver option

  For example, for BCS Class I-based biowaiver

  – *A waiver request of in vivo testing for all the strengths of this product may be considered provided that the appropriate documentation regarding high solubility, high permeability and rapid dissolution as detailed in the most recent version of the FDA guidance for industry on M9 Biopharmaceutics Classification System-Based Biowaivers is submitted in the application.*

  – *Applicants may use the information contained in the approved labeling of the RLD. Peer reviewed articles may not contain the necessary details of the testing for the Agency to make a judgment regarding the quality of the studies. A decision regarding the acceptability of the waiver request can only be made upon assessment of the data submitted in the application.*

- For highly variable drugs – included use of a reference-scaled average BE approach (e.g., selegiline HCl, ODT)

https://www.fda.gov/media/148472/download;
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021479.pdf

Other Safety-Related Revisions to PSGs

- Reassessment of REMS Recommendations to previously posted PSGs
  - Addition of REMS language (10 PSGs) – opioid analgesic REMS shared system
    - e.g., Oxycodone HCl tablet is under a REMS with ETASU. All pertinent elements of the REMS/ETASU are recommended to be incorporated into the protocol and informed consent
  - Removal of REMS language (4 PSGs) – REMS or ETASU no longer required or recommended
  - Editorial (10 PSGs)
- Change of study population due to embryo-fetal toxicity and fertility concerns
  - e.g., Healthy males and non-pregnant females, general population → Healthy males not of reproductive potential and females not of reproductive potential

ETASU: Elements to Assure Safe Use; https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/risk-evaluation-and-mitigation-strategy-rems-public-dashboard

Future PSG Considerations

- Ongoing additional assessment including the following:
  - pH-dependency
  - Dose or strength to be studied
    - 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
  - Analyte(s) - parent and metabolite recommendation
  - Liquid-filled lipid-based capsules, solid dispersion
- Study population from patients to healthy subjects
  - Some different recommendations are noted from other agencies' guidelines
  - Types of studies (fasting or fed) including a type of meal (high- or low-fat)
- Specific subsets of healthy subjects (e.g., sex, age, menopausal status, reproductive potential, etc.)

Considerations for M13A and PSGs

- Some of the previously published PSGs were not revised, and they continue to reflect the FDA's current thinking
  - High-Risk drugs with one study recommendation
  - PSGs with patient-based BE study recommendation
  - Drugs showing less than proportional increase with increasing dose due to solubility or if proportionality is unknown

- FDA will forecast the future revisions with category and a brief description where applicable

Considerations for M13A and PSGs

FDA PSGs: *In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended, but not required.*

- Currently published PSGs reflect the FDA's current thinking and therefore, prospective ANDA applicants can utilize the PSG recommendations
- Alternative approaches from M13A guidance and PSG recommendations may be acceptable if appropriate scientific justification is provided

Seeking FDA's Advice

- If applicants propose an alternative method different from the guidance, applicants can provide justification, submit controlled correspondence or request meetings through appropriate pre-ANDA or ANDA meetings, e.g., PSG teleconferences and PSG meetings as applicable

- PSG Teleconferences (pre-submission PSG teleconference to CDER Direct Next Gen Collaboration Portal (https://edm.fda.gov) or post-submission PSG teleconference to Enterprise Submission Gateway (eCTD submission)

https://www.fda.gov/media/164111/download; https://www.fda.gov/media/107626/download; https://www.fda.gov/media/165468/download

PSG-Related Communications

- Upcoming PSG Forecast Website
  - Provides information related to upcoming new and revised PSGs in the next 12 months (active ingredient, route of administration, dosage form, RLD or RS number, product complexity, planned publication, updates)
- Public comments on PSGs
  - FDA issues a Federal Register Notice announcing the availability of new and revised PSGs via Docket Number FDA-2007-D-0369
  - Comments can be submitted electronically to the docket or by mail

https://www.fda.gov/drugs/guidances-drugs/upcoming-product-specific-guidances-generic-drug-product-development; https://www.regulations.gov/support

Challenge Question

What is the expected impact of the final M13A guidance on BE studies for generic drugs?

A. Reduced number of studies recommended

B. Increased emphasis on in vitro BE studies

C. More stringent criteria for BE acceptance

D. No significant changes to current BE study protocols

Key Takeaways (1)

- ICH M13A, the first harmonized ICH guideline that focuses on BE, has been finalized, adopted by ICH, and is ready for implementation by ICH regulatory members, including FDA and other global regulatory agencies (in *Step 5*)
- Impacts a significant portion of the pharmaceutical market
  - IR products account for ~46% of approved new drugs in the U.S.
- Reduces the need for additional in vivo BE studies due to divergent regulatory recommendations prior to harmonization
- Supports streamlined global drug development
- Benefits patients by increasing access to generic drugs

Key Takeaways (2)

- FDA implements M13A by updating the relevant guidance documents to align with the recommendations in M13A final guidance
  - PSGs for ANDAs have been updated
    - Initial revisions focused on removing one BE study for non-high-risk products
  - Updated general BE guidance will be published in 2025
- FDA's current practice and M13A offer flexibility
  - Prospective ANDA applicants may provide appropriate scientific justification, if they propose an alternative approach and deviate from the guidance recommendations
  - Applicants may communicate with FDA through meetings or controlled correspondences

Resources

- FDA Final Guidance: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms (Oct 2024)
- FDA Final Guidance: M13A Bioequivalence for Immediate-Release Solid Oral Dosage Forms Questions and Answers (Oct 2024)
- ICH M13A Step 4 Presentation (July 2024)
- 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)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