Global Harmonization of Immediate-Release Solid Oral Drug Product Bioequivalence Recommendations and the Impact on Generic Drug Development

Joseph Kotsybar, PharmD[a], Susan Hakeem, PharmD[a,b], Lei Zhang, PhD[a], Wenlei Jiang, PhD[a*]

[a]Office of Research and Standards, Office of Generic Drugs, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland 20993
[b]Current affiliation: Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology, U.S. Food and Drug Administration, Center for Drug Evaluation and Research, Silver Spring, Maryland 20993
*Corresponding Author (Wenlei.jiang@fda.hhs.gov)

Introduction

- Solid oral drug products are commonly administered as immediate-release (IR) products that instantly disintegrate and release their active pharmaceutical ingredient (API) popularizing them as a common therapy option.
- Different regulatory agencies have inconsistent recommendations for bioequivalence (BE) studies and criteria for generic drug approval for solid oral IR drug products.
- The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) seeks to harmonize BE standards for generic drugs beginning with a guideline on IR oral solid dosage form drug products (ICH M13A), draft published December 2022.
- To support this effort, this study aimed to:
  - Develop a full representation of the FDA's current approved oral IR drug product landscape categorizing oral IR products into solid, liquid (solution/suspension), or semi-solid dosage forms
  - Evaluate the current BE methods recommended by the U.S. FDA and highlight key differences between FDA and EMA
  - Demonstrates how M13A could harmonize BE recommendations for IR solid oral products to facilitate global drug development and improve patient access to affordable medications globally

Materials and Methods

- U.S. FDA-approved drug product information was obtained via the Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, as well as Drugs@FDA, from January 1938 to December 2022
  - Reference listed drug (RLD) products with multiple strengths were grouped together and counted as one drug product in the analysis.
- All approved IR solid oral products were categorized and further characterized to specific dosage forms based on United States Pharmacopeia (USP) ⟨1151⟩ Pharmaceutical Dosage Forms General Chapter.
  - Already prepared liquids, such as solutions, suspensions, and emulsions, as well as semi-solid dosage forms such as oral pastes and chewable gums, were excluded in our further analysis.
- Published PSGs for IR solid oral products were obtained through the FDA's PSG database from September 2008 to December 2022 and the EMA's website from January 2009 to December 2022.

Risk-based determination on the need to conduct BE studies under both fasting and fed conditions or one condition only (fasting or fed) as recommended by ICH M13A will significantly reduce the number of BE studies to be under both conditions for generic IR solid oral drug product development compared to the current FDA recommendations, thus shortening development duration and lowering study costs.

Figure 1. Immediate-Release Solid Oral Drug Product Landscape (Based on U.S. FDA-Approved New Drug Applications) (1938-2022)

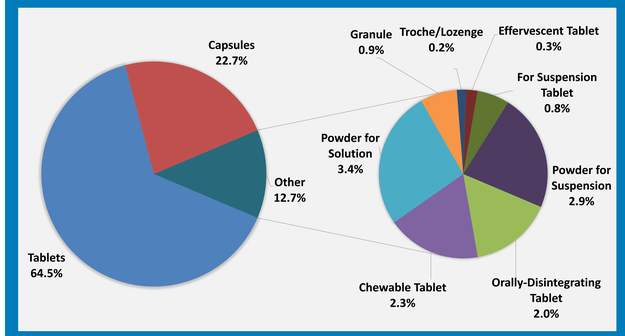
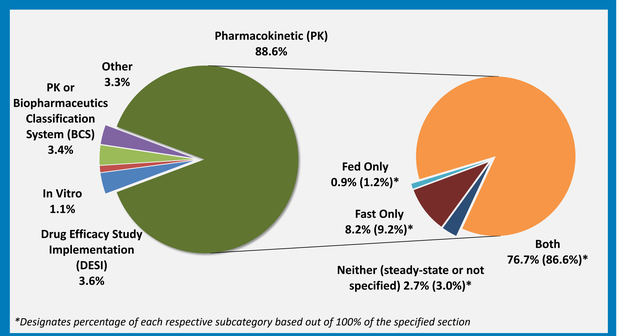


Figure 2. Bioequivalence Recommendations in FDA Product-Specific Guidances for Immediate-Release Solid Oral Products



**Designates percentage of each respective subcategory based out of 100% of the specified section*

Table 1. Recommendation on Drug Administration in U.S. FDA and EMA Product-Specific Guidances for Specialty Immediate-Release Solid Oral Drug Products

Dosage Form	Dosage Form Description	Special Administration Considerations in U.S. FDA PSGs**	Special Administration Considerations in EMA PSGs
Orally-Disintegrating Tablet	• Solid oral dosage form containing medicinal substances that disintegrate rapidly, usually less than 30 seconds, when placed upon the tongue	• Per PSGs, patients advised to either take with or without water based on RLD labeling • If labeling indicates with or without water, PSG will indicate to take without water	• Other Critical aspects: intake without water for the orodispersible tablets
Chewable Tablet	• Solid oral dosage form intended to be chewed and swallowed; designed to be palatable and crushed • Potential to be swallowed whole, impacting bioavailability and the patients' drug levels	• When RLD labeling states, the tablet must be chewed before swallowing, the PSG will indicate the products should be chewed when administered • When RLD labeling give options, PSG will indicate the product should be swallowed whole, with 240 mL of water	• No PSG for oral chewable tablets
Effervescent Tablet	• Solid oral uncoated tablets containing acidic excipients and carbonates that react rapidly when placed in water	• All effervescent products are added to liquids before drug consumption • Patient consumes drug after dissolution of drug into a solution, leaving no residue.	• No Critical Aspects
Granule	• Solid oral dosage form containing particles which have been aggregated to form large granular material with diameter of approximately 2-4 mm	• Granules are generally required to be administered with soft food before consumption • Effervescent granules require mixing with liquids rather than food	• No Critical Aspects
Powder	• Solid oral dosage form containing dry mixtures of finely divided, crushed, or grinded, medicinal substances varying from 10 nm-1000 µm	• Oral powder generally is combined on with liquids before consumption • Some products require food specific combination due to poor solubility • Some products require neither food nor liquids during administration	• No Critical Aspects

Table 2. Comparison of Current FDA and EMA BE Guidances' for IR Solid Oral Drug Products

	U.S. FDA	EMA
General guidance regarding PK BE study fasting/fed recommendations	FDA generally recommends both a fasting and fed BE study	Conducted under fasting conditions; Fed BE study is recommended based on labeling recommendations or specific formulation characteristics
General guidance regarding PK BE study subject selection	Generally performed in healthy subjects, unless the drug carries safety concerns that make this approach unethical	
PSGs published as of 12/31/2022	1051	63
PSGs recommending in vivo PK endpoint studies	88%	100%
PSGs recommending both fasting/fed BE studies	86.6%	15.9%
PSGs recommending fasting BE study only	9.2%	69.8%
PSGs recommending fed BE study only	1.2%	14.3%
PSGs recommending healthy subjects	94.3%	92.1%
PSGs recommending patient subjects	5.5%	7.9%

***Recommendations in PSGs are in general aligned with the FDA Draft Guidance, Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (Aug 2021).*

Results and Discussion

- Over 80% of all oral IR product NDAs currently listed in Orange Book fall within the scope of ICH M13A
  - Over 20 different oral IR dosage forms with approximately 2,000 unique APIs
- Majority of U.S. FDA published PSGs for IR solid oral products (about 87%) recommend both a fasted and fed BE study (Table 2), aligning with FDA's draft guidance for industry, 'Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application' (Aug 2021)
- Available EMA-published PSGs reflect their overall guideline, as 69.8%, 14.3%, and 15.9% recommended a fasting BE study only, a fed BE study only, and both fasting and fed studies, respectively (Table 2).
  - EMA's 'Guideline on the Investigation of Bioequivalence' (2010) states the BE study should be typically conducted under fasting conditions, but the number of studies and study design can vary depending on the physicochemical characteristics of the drug
- ICH M13A guideline harmonizes food intake conditions for BE studies using a risk-based approach
  - Most IR oral drug products are designated as "non-high-risk" products and BE may be demonstrated in a fasting BE study
  - "High-risk" products where complex formulation or manufacturing process will likely impact in vivo performance based on variable GI conditions, both fasting and fed studies are recommended
- ICH M13A also provides specific instructions regarding study population and administration of water and food based on product labeling
  - FDA PSGs include standard administration instructions in line with current ICH M13A recommendation in comparison to EMA PSGs
  - EMA and FDA general BE guidances are consistent with ICH M13A recommendations; studies should generally be performed in healthy subjects, unless the drug carries safety concerns

Table 3. Direct Comparison of IR Solid Oral Drug Product PSGs***

EMA PSGs not having comparable U.S. FDA PSG	6%
EMA and FDA PSGs aligning on PK study fasting/fed recommendation	26%
EMA and FDA PSGs not aligning on PK study fasting/fed recommendation	68%
EMA and FDA PSGs aligning on PK study subject selection	84%
EMA and FDA PSGs not aligning on PK study subject selection	10%

****% based on total number of PSGs published by EMA on 12/31/2022: 63*

Conclusion

- This work provides a comprehensive landscape of all FDA-approved oral IR drug products.
- Once FDA PSG recommendations are aligned with ICH M13A, eliminating in vivo fed BE studies for most IR solid oral products, there will be significant savings in both costs and time for generic drug development, increasing generic drug access to patients.