A Comparative Review of Study Population and Dose Recommendations for In Vivo Bioequivalence Studies with Pharmacokinetic Endpoints between FDA and EMA Guidances

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Background and Purpose

The U.S. Food and Drug Administration (FDA)'s product-specific guidances (PSGs) describe the Agency's current thinking on the most appropriate method for establishing therapeutic equivalence between generic drugs and reference listed drugs (RLDs). The European Medicines Agency (EMA)'s product-specific bioequivalence (BE) guidances summarize the relevant study design principles for demonstration of BE. Understanding the major areas of difference in recommendations on BE study design between FDA's and EMA's guidances is important to address challenges from generic drug developers seeking approval from both agencies. Efforts toward global harmonization include the adoption of International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (M13A) guideline, which may resolve some differences in study design. This study evaluated the underlying factors leading to differences in recommendations on study population and dose for BE studies with pharmacokinetic (PK) endpoints for oral immediate-release (IR) drug products.

Methods

A list of EMA's product-specific BE guidances of oral IR drug products were retrieved from the EMA website. Subsequently, the corresponding PSGs for products with the same active pharmaceutical ingredients (APIs) and dosage forms were retrieved from the FDA PSG website. The recommended study population, dose, and study design in these guidances were then compared for each drug product. Information on the highest approved strength was retrieved from the respective agencies' approved labeling or product information. Reviews from FDA and public comments from EMA were collected to identify rationales supporting the recommendations.

Results

- Seventy-eight oral IR drug products (66 APIs) have PSGs available from both agencies (66 from EMA, 78 from FDA) as of March 2024.
- Of guidances for the 78 drug products, 5 have differences in the recommended study population **(Figure 1)**. (Refer to Poster#23 for differences related to study type)
- FDA recommends patients for in vivo PK BE studies of three drug products while EMA recommends healthy volunteers (HVs). For asenapine sublingual (SL) tablet, FDA recommends patients while EMA recommends either HVs or patients, due to tolerability concerns. For lapatinib tablet, FDA recommends HVs while EMA recommends patients **(Table 1)**.
- In general, risks due to toxicities including carcinogenicity, hemodynamic effects, cardiotoxicity, and/or hepatotoxicity, were considered for the recommendation of the appropriate study population.
- The guidances recommend a different study dose in HVs for 13 drug products (11 EMA and 13 FDA product-specific [BE] guidances).
- Four EMA guidances (dolutegravir tablet, elvitegravir tablet, rivaroxaban tablet, and sirolimus tablet) recommend BE studies using more than one strength in HVs due to PK characteristics (e.g., non-dose-proportionality or differential food-effect) while FDA recommends a single strength **(Figure 1)**.
- Of the nine guidances with differences in study dose recommendation, EMA recommends a study dose equal to the highest single unit strength for all except for bosutinib. Compared to the highest approved single unit strength, FDA recommended a lower study dose for four, equal to for four, and higher than for one drug product **(Figure 2)**.
- When compared between the agencies, FDA recommends a relatively higher dose for two drug products and EMA recommends a relatively higher dose for seven drug products **(Figure 2)**.

Results (cont.)

Figure 1. Identified Differences Between EMA and FDA Product-specific (BE) Guidances

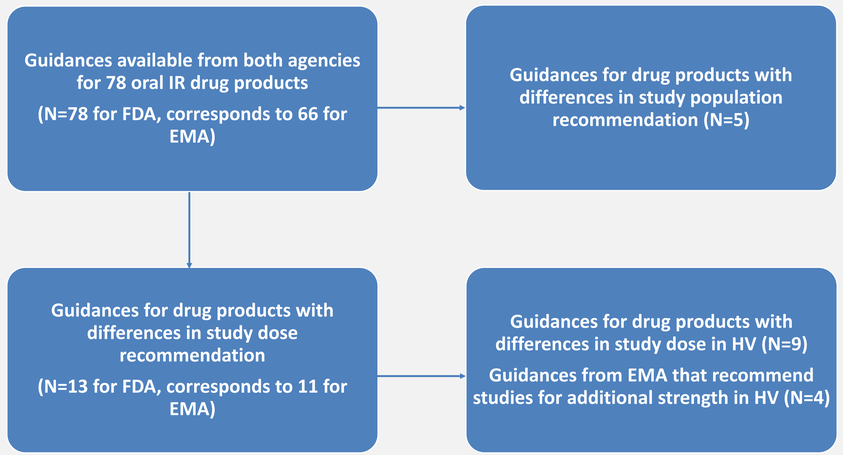
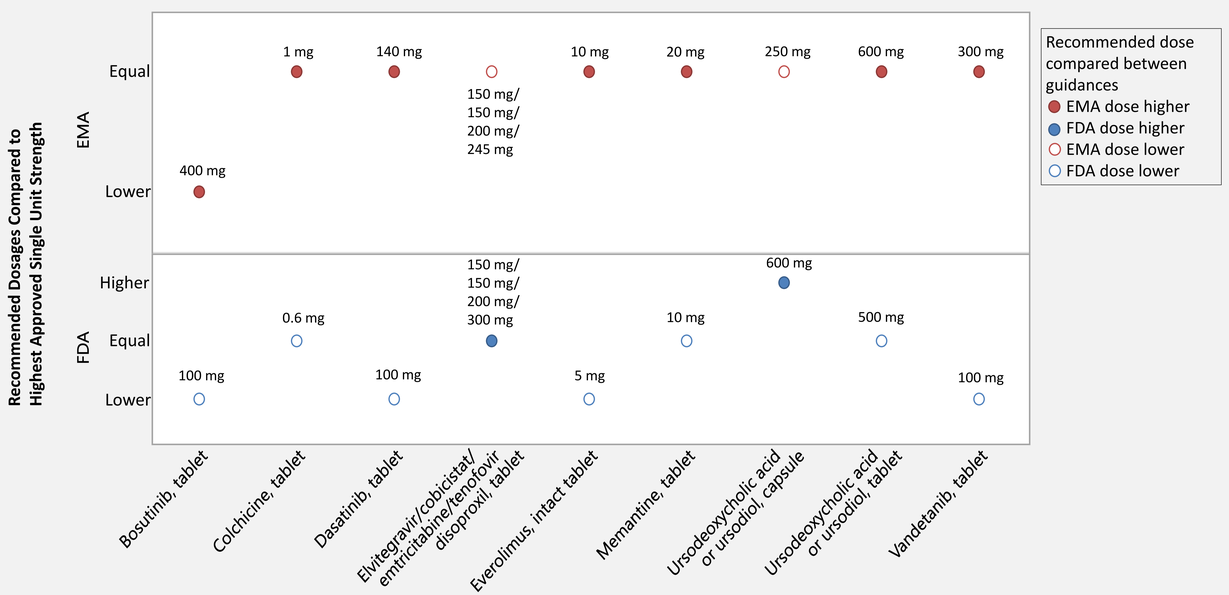


Table 1. Differences in Study Population Recommendation and Study Design

Drug Product	FDA PSG			EMA Product-Specific BE Guidance		
	Date Recommended	Study Population	Study Design	Effective Date	Study Population	Study Design
Asenapine, SL tablet	Nov 2018	Patients	Multiple-dose, cross-over	Nov 2016	HVs or Patients (in case of intolerability)	Single dose, cross-over
Imatinib, tablet	Jul 2014	Patients	Multiple-dose, cross-over	Oct 2015	HVs	Single dose, cross-over
Lapatinib, tablet	Nov 2022	HVs*	Single dose, cross-over	Apr 2022	Patients**	Multiple dose, cross-over
Pazopanib hydrochloride, tablet	Mar 2021	Patients	Multiple-dose, cross-over	Jul 2017	HVs	Single dose, cross-over or parallel
Sunitinib malate, capsule	Apr 2010	Patients	Multiple-dose, cross-over or parallel	Dec 2015	HVs	Single dose, cross-over

*Revised from patients to HVs; **Revised from HVs to Patients

Figure 2. Recommended Study Dose Compared Between Agencies and Highest Approved Single Unit Strength



Conclusion

- This survey identified the differences in study population (HVs vs patients) and dose for PK BE studies between EMA and FDA product-specific (BE) guidances.
- Each agency's recommendations appear to be determined based on their perspectives on safety and (or) biopharmaceutical assessment of each drug product at the time of publication. Of note, recommendations have been revised for certain drug products based on accumulated safety information (e.g., study population of lapatinib and pazopanib).
- The differences in the recommended study dose may be attributed to either variations in approved strengths or in their safety assessment, and may reflect differences in the current general BE guidances between FDA and EMA.
- Implementation of ICH M13A is expected to result in revised PSGs to minimize differences between the agencies. Some observed differences for a specific product may need continuing and additional efforts to understand the reasons behind them to help harmonize the recommendations among regulatory agencies and facilitate generic drug development.

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Disclaimer

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