FDA and EMA Regulatory Recommendations on Fed Bioequivalence Study in Healthy Subjects vs. Patients for Generic Drug Development

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Background and Purpose

Global generic applicants seeking approvals by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) may face challenges due to discordances between the two agencies in recommendations for bioequivalence (BE) studies in product-specific (BE) guidances. In July 2024, the ICH M13A guideline was published to harmonize recommendations on conducting BE studies for immediate-release (IR) solid oral dosage forms. This guideline includes a risk-based approach to determine the type of BE study with regard to food. This survey aimed to elucidate the scope of discordances between the two agencies (prior to the implementation of the harmonized guidance) on recommendations for the type of study (i.e., food condition) stratified by study subjects (healthy volunteers [HVs] vs. patients) in *in vivo* pharmacokinetic (PK) BE studies for IR oral drug products.

Materials and Methods

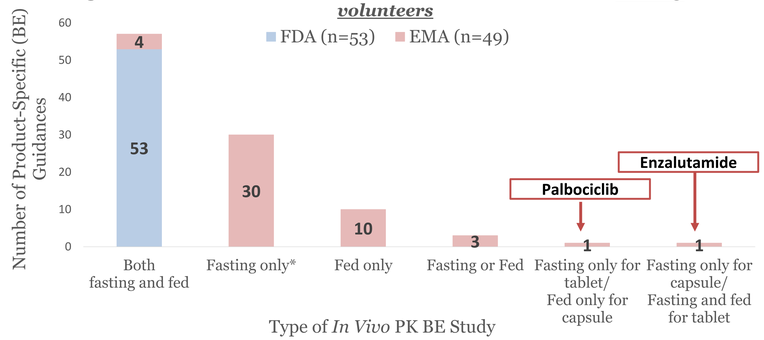
The EMA webpage was reviewed to generate a list of product-specific BE guidances for oral IR drug products with corresponding FDA PSGs. Respective agencies' recommendations for each drug product on the type of study with respect to food (i.e., fasting or fed), dose, study subjects, additional *in vivo* BE studies, and options to waive an *in vivo* study were reviewed along with their rationale supporting the recommendations.

Results

- As of March 2024, 66 EMA product-specific BE guidances for oral IR products had corresponding FDA PSGs (n=78).* Of these, 52 had corresponding FDA PSGs (n=59) with at least one discordance in study design or study subjects.
- In guidances where both agencies recommend HVs, FDA recommends both fasting and fed studies (n=53), while majority of the EMA guidances recommend a single study under the specified food condition (n=44; fasting or fed) and only five guidances from EMA recommend both fasting and fed studies (**Figure 1**).
- Both agencies recommend BE studies in patients for two drug products (olaparib tablet, vemurafenib tablet), and they have discordant recommendations on the type of study (**Table 1**).
- For five guidances (asenapine sublingual [SL] tablet, imatinib mesylate tablet, lapatinib ditosylate tablet, pazopanib hydrochloride tablet, sunitinib malate capsule), FDA and EMA recommend different study subjects (HVs vs. patients). In guidances where BE studies are recommended in patients, EMA generally specifies the type of study including meal type based on the complexity of formulation design whereas FDA recommends one study without specifying the food condition or instructs to follow the labeling recommendation.
- In guidances where both agencies recommend BE studies in HVs, additional discordances were identified with respect to recommended strength for each study type and option for in vivo study waiver (**Table 2**).
- In EMA guidances where both fasting and fed studies are recommended due to formulation characteristics (e.g., olaparib tablet, enzalutamide tablet), a waiver option for the fed study is available if a test product is manufactured using the same manufacturing technology and if excipients that may affect bioavailability are qualitatively (Q1) the same and quantitatively (Q2) similar between test and reference products.
- Furthermore, for guidances of dabigatran capsule and prasugrel tablet, an additional study with a proton-pump inhibitor (PPI) to assess BE under the elevated gastric pH is recommended by EMA, but not by FDA (**Table 3**).

Results (cont.)

Figure 1: Type of study regarding food condition in product-specific (BE) guidances where both FDA and EMA recommend studies in *healthy volunteers*



*Asenapine SL tablet: either HVs or patients are acceptable from EMA

Table 1: Type of study and rationales in product-specific (BE) guidances where both FDA and EMA recommend studies in *patients* (n=2)

Drug Product	FDA	EMA	
	Type(s) of Study	Type(s) of Study	Rationale for EMA's BE Recommendations
Olaparib, tablet	1 MD study Unspecified food condition	2 MD studies Fasting (non-strict) and fed (light-meal)*	Formulation characteristics (i.e., solid dispersion)
Vemurafenib, tablet	1 MD study Unspecified food condition	1 MD study Fed only	Pronounced food effect

Abbreviations: MD = multiple dose; SD = single dose;
*Fed study may be waived if using the same manufacturing technology and if excipients are Q1 same/Q2 similar between test and reference products

Table 3: Product-specific (BE) guidances recommending an additional study with a PPI-in *healthy volunteers* (n=2)

Drug Product	FDA	EMA	
	Type(s) of Study	Type(s) of Study	Rationale for EMA's BE Recommendations
Dabigatran etexilate, capsule	2 SD studies Fasting and fed No PPI study	2 SD studies Regular fasting study and fasting PPI study	Formulation characteristics (i.e., pH dependent drug substance)
Prasugrel hydrochloride, tablet	2 SD studies Fasting and fed No PPI study	1 SD study Fasting only An additional study under elevated gastric pH (i.e., fed or with PPI) if the test product contains a different salt form or the free base of prasugrel	Different pharmaceutical forms

Abbreviations: SD = single dose;

Table 2: Additional discordances identified in the type of study for product-specific (BE) guidances recommending *healthy volunteers*

Drug Product	FDA	EMA	
	Type(s) of Study	Type(s) of Study	Rationale for EMA's BE Recommendations
Rivaroxaban, tablet	Fasting and fed at 20 mg	Fasting at 10 mg Fed at 20 mg	Different food effect resulting in different food recommendations for the lower (2.5 and 10 mg) and the higher (15 and 20 mg) strengths: Fasting study for the lower strengths, and fed study for the higher strengths; Highest strengths (10 mg and 20 mg) used for a drug with linear PK and low solubility
Sirolimus, tablet	Fasting and fed at 2 mg	Fasting and fed at 2 mg Fasting and fed at 0.5 mg	Formulation characteristics (i.e., nanotechnology); Non-dose-proportionality and limited information about worse-case condition to detect BE
Enzalutamide, tablet	Fasting and fed at 80 mg No comment on fed study waiver	Fasting and fed at 80 mg Fed study may be waived if using same manufacturing technology and if excipients that might affect bioavailability are Q1 same/Q2 similar between T and R products	Formulation characteristics (i.e., solid dispersion)

Conclusion

- This survey identified specific oral IR products with discordances in current recommendations on the type of BE study between FDA and EMA.
- Most discordances are reflected in whether BE studies in HVs should generally be performed under both fasting and fed conditions or one condition only.
- Additional discordances identified are the type of study recommended in patients, selection of study dose across the recommended studies, option for *in vivo* study waiver, and recommendation for additional study with a PPI.
- Each agency's product-specific (BE) guidances are in general aligned with their respective current general BE guidances of FDA and EMA, and appear to be based on their current perspectives on formulation characteristics, adequacy of BE data, and practicalities of conducting BE studies.
- Most discordances observed are anticipated to be resolved once the ICH M13A guideline is implemented and affected PSGs are revised to align with M13A.
- This comparative analysis would help to understand the areas of discordances along with their rationale, which can contribute to improving the harmonization of the recommended study design among the regulatory agencies and facilitating global generic drug development.

*Refer to Poster #A002 for comparison of the recommended study population/dose

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