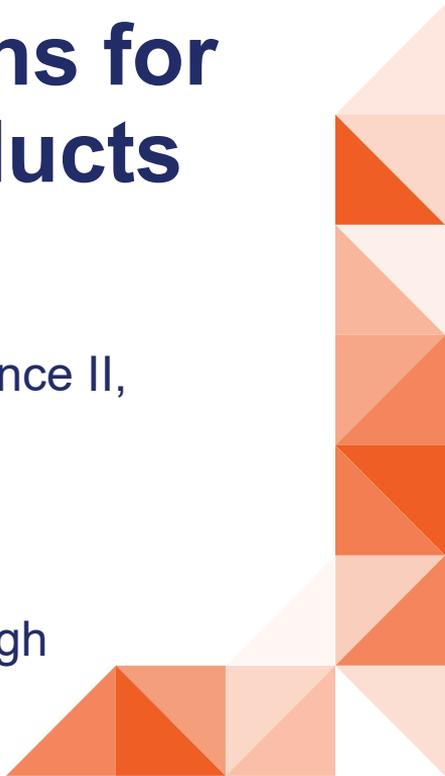


Beyond General Guidance: Tailored PSG Recommendations for Immediate Release Drug Products

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[Facilitating Generic Drug Product Availability Through
Product-Specific Guidance] – April 25, 2024



Objectives

- Discuss product-specific guidance (PSG) considerations for immediate release (IR) drug products
- Understand the need for developing tailored PSG recommendations and discuss these tailored PSG recommendations through case studies
- Learn about strategies for implementing tailored recommendation

General PK Endpoint BE Guidance



Draft Guidance For Industry: *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021)¹

- Provides recommendations to applicants planning to include pharmacokinetic (PK) bioequivalence (BE) information in abbreviated new drug applications (ANDAs) and ANDA supplements
- Applicable to IR and modified release (MR) dosage forms, and non-orally administered drug products in which reliance on systemic exposure measures is suitable for establishing BE

¹ <https://www.fda.gov/media/87219/download>

Product-Specific Guidances

- Reflects the FDA's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs (RLDs)²
- For all published PSGs for oral IR drug products, in vivo BE studies with PK endpoints account for 88% of BE approaches recommended³

² [Product-Specific Guidances for Generic Drug Development | FDA](#)

³ Kotsybar, J, Hakeem, S, Zhang, L, Jiang, WL, 2023, Clinical and Translational Science, 16 (12): 2756-2764

What Considerations are Included in PSG Recommendation for PK BE Studies?

- Include
 - Indication, Dosing Regimen, Administration, and Safety Information
 - Biopharmaceutics Classification System (BCS)
 - Drug Product Design
 - Food and Anti-Acid Effects
 - Dose Proportionality/PK linearity
 - Parent vs Metabolites
 - Bioanalytical Sensitivity

Identify the Need for Developing Tailored PSG Recommendations



- Complexity
 - Complex Drug Substances
 - Complex Drug Products
 - Alternative BE Study Design [study design, strength and dose, conditions, study population, BE analytes, etc.]
 - Alternative BE Approaches [BCS-based waiver, PK or comparative clinical endpoint BE studies, modeling, approval pathway (e.g., suitability petitions), etc.]

Study Strength and Dose

- General PK BE Guidance: *Generally, the highest-marketed strength can be administered as a single unit*
- The highest strength as single unit is applicable to all IR dosage forms
 - tablets, capsules
 - orally disintegration or chewable tablets
 - granules, granules/powders for oral suspension
 - oral suspensions
 - oral solution and liquid

Cases When Using a Single Unit is Not Feasible and Possible Solutions

- When single unit use is not feasible:
 - If it's concentrated suspension
 - If there are bioanalytical sensitivity issues
- Possible solution:
 - Multiple units of the highest-marketed strength can be administered, provided that:
 - The total single dose remains within the labeled dose range, or
 - The total dose is safe for administration to the study subjects

Cases When the Highest Strength Cannot Be Used and Alternative Approaches



- Cases when the highest strength cannot be used:
 - If the highest strength is not safe for healthy subjects
- Alternative approaches
 - The study can be performed with patients already prescribed and taking the drug at the highest-marketed strength
 - Alternatively, the study can use a lower strength in healthy subjects, where appropriate

Cases When BE Studies for High and Low Strengths May Be Recommended



- Cases recommending BE studies for high and low strengths:
 - If the PK are nonlinear
 - If there are significant differences in product formulation for different strengths
- Recommended approach:
 - Employ the bracketing approach by conducting BE studies on both high and low strengths to demonstrate BE

Case Study 1: Gabapentin Tablets

- PSG recommendations⁴
 - Fasting and Fed BE studies on 900 mg strength
 - Fed BE study on 300 mg strength
 - Waiver request of in vivo testing: 450 mg, 600 mg, and 750 mg strengths
 - Comparative multi-media in vitro dissolution testing
 - In vitro alcohol dose dumping testing

⁴https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_022544.pdf

Case Study 1: Gabapentin Tablets

- Rationale for recommending PK BE studies for both high and low strengths
 - Bioavailability is not dose proportional, as the dose is increased, bioavailability decreases
 - The formulation features a gastric retentive drug release mechanism and the time to reach maximum plasma concentration (T_{max}) is 8 hours, approximately 4-6 hours longer than gabapentin conventional immediate release formulation
 - The formulation lacks compositional proportionality and there are significant differences in product formulation for different strengths

Case Study 2: Levothyroxine Capsules



- PSG recommendations⁵
 - Fasting BE study on 0.2 mg strength at a dose of 0.6 mg
 - Bioequivalence based on (90% CI): Baseline-corrected levothyroxine
 - Waiver request of in vivo testing: 11 lower strengths

⁵https://www.accessdata.fda.gov/drugsatfda_docs/psg/Levothyroxine_Sodium%20capsules_NDA%20021924_RC%20Oct%202018.pdf

Case Study 2: Levothyroxine Capsules



- Rationale for recommending multiple units of the highest strength
 - Levothyroxine capsules is L-thyroxine (T4) indicated for adults and pediatric patients 6 years and older with hypothyroidism
 - To ensure adequate measurement of T4 concentrations, using multiple units of the highest strength is recommended
 - The total BE dose represents the maximum recommended dose, supported by evidence of both safety and effectiveness

Analyte to Be Measured: Parent vs. Active Metabolites



- General PK BE Guidance: *FDA generally recommends that applicants measure only the parent drug, rather than metabolites. FDA recommends that applicants analyze the parent drug measured in these BE studies using a confidence interval approach*
- Scientific justification on the choice of analytes:
 - Sensitivity to detect changes in formulation performance
 - Clinical significance
 - Prodrug considerations
 - Analytical advances in analytical technology

Cases When Metabolite Data May Be Recommended for BE Demonstration



- If parent drug concentrations are too variable to allow reliable bioanalytical measurement (e.g., prodrugs are rapidly eliminated resulting in difficulties in demonstrating BE based on parent drug data).
- If primary metabolite(s) (1) form substantially through pre-systemic metabolism (gut wall or gut lumen metabolism) and (2) contribute significantly to the safety and/or efficacy of the product

Case Study 3: Ezetimibe Tablets

- PSG recommendations⁶
 - Analytes to measure: ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe glucuronide) in plasma
 - BE based on (90% CI): ezetimibe (unconjugated) and total ezetimibe (ezetimibe + ezetimibe glucuronide)

⁶https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ezetimibe_tab_21445_RC10-08.pdf

Case Study 3: Ezetimibe Tablets

- Rationale for recommending total ezetimibe as the BE analyte
 - Ezetimibe undergoes extensive pre-systemic metabolism to ezetimibe-glucuronide and is subject to enterohepatic recycling, including hydrolysis of ezetimibe-glucuronide back to ezetimibe
 - Literature findings underscore the significance of measuring total ezetimibe as a BE analyte

Types of BE Studies

- Include
 - Single-dose fasting studies
 - Single-dose fed studies
 - Multiple-dose studies
 - In vitro studies (e.g., dissolution)
 - Comparative clinical endpoint BE studies
 - Biowaivers
 - Cross-referencing BE studies

Cases When an Additional Type of BE Study May Be Recommended



- Include
 - Special or complex formulation design
 - Solid dispersion
 - Lipid-based formulation
 - Nanotechnologies (e.g., micro/nano-emulsions)
 - Gastro-retentive formulation
 - Polymer-based coating
 - Acid modifier
 - Other dosage forms
 - Complex drug products

Case Study 4: Palbociclib Tablets

- PSG recommendations⁷
 - Three in vivo BE studies with PK endpoints:
 - Fasting
 - Fed
 - Fasting in presence of an acid reducing agent (ARA), e.g., proton pump inhibitor (PPI)

⁷https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_212436.pdf

Case Study 4: Palbociclib Tablets



Rationale for an ARA BE study	Capsules (approved in 2015)	Tablets (approved in 2019)
Solubility	Low solubility pH dependent at pH 6.8	
Dissolution	< 20% at pH 6.8	↑ 50% at pH 6.8
Formulation	No acid modifier	Contain 10% succinic acid
ARA effect under fasting condition	Observed	Not observed
Labeling-ARA	Allow use of ARA with food	Allow use of ARA without regard to food

Strategies for Implementing Tailored PSG Recommendations



- Working to refine the general BE guidance
- Updating risk assessment framework to incorporate these tailored recommendations
- Communicating with industries through various mechanisms to ensure that tailored recommendations are understood and followed effectively

Challenge Question

Which of the following statements is **NOT** true?

- A. Most PSGs recommend a highest available strength (as a single unit) and do not specify the dose.
- B. In most cases, complex drug products or complex BE issues require tailored PSG recommendations that are out of the scope of general PK BE guidance.
- C. Alternative BE approaches include in vitro, in vivo, and modeling approaches
- D. PSG recommendations only include fasting and/or fed BE studies

Questions?

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