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

Learning 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Draft Guidance For Industry: *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA* (August 2021)[1]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 recommended[3]

[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*
- Is the highest strength as single unit 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 recommendations[4]
  - 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

[4] https://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 (Tmax) 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 recommendations[5]
  - 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

[5] https://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 challenges and 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 presystemic 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 recommendations[6]
  - 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)

[6] https://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 recommendations[7]
  - 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)

[7] https://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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