Product-Specific Guidances in Action:

Key Lessons and Common Questions in Oral Drug Products

Myong Jin Kim, Pharm.D., FCP

Director
Division of Therapeutic Performance II, Office of Research and Standards

Office of Generic Drugs
CDER | U.S. FDA

Generic Drugs Forum – April 22, 2026

Learning Objectives

- Discuss FDA's key updates and proactive approaches in PSG development of oral drug products
  - M13A implementation of IR drug products
  - BCS-based biowaiver options
  - Suitability petitioned dosage forms and strengths
  - Cross-referencing approaches
  - NTI drugs
- Discuss FDA's efforts for increased transparency in PSGs

PSG: product-specific guidance; M13A: Guidance for Industry - M13A bioequivalence for immediate-release solid oral dosage forms; IR: immediate release; BCS: biopharmaceutics classification system; NTI: narrow therapeutic index; https://www.fda.gov/media/165049/download

FDA's Efforts in Implementing M13A into PSGs Since Oct 2024

- Assessed risk evaluation for "High-Risk" and "Non-High-Risk" for IR drugs products
  - The most significant change to PSGs **(2 BE studies to 1 BE study)**
  - Of ~1340 oral IR PSGs, about 77% recommend **1 BE study** (either fasting or fed)
  - reduce the need for additional in vivo BE studies and support streamlined global drug development

BE: Bioequivalence; https://www.fda.gov/media/165049/download

BCS-based Biowaiver and PSGs

- **BCS-based biowaiver options**
  - In general, a BCS-based biowaiver option is included in PSGs when the Agency has determined that a drug product is either BCS I or III
  - A waiver request of in vivo testing based on its BCS class I or III
  - Useful option especially in lieu of patient-based BE study (typically a steady state PK or comparative clinical endpoint)
- **BCS-based biowaiver as an alternative approach**
  - Products that *may be eligible* for a BCS class III-based biowaiver
  - Applicants are encouraged to consider this approach by submitting the relevant information in ANDAs

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208462.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020151.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_218944.pdf; PK: pharmacokinetics; ANDA: abbreviated new drug application

Proactive Approaches: Suitability Petition and PSGs

- In general, most experiences with petitions related to a different dosage form (e.g., tablet to ODT)/strength (additional strength(s))

- Historically, new dosage form and strengths approved under a suitability petition were not updated in PSGs until a petitioned ANDA has been approved

- FDA is proactively incorporating recommendations for petitioned dosage forms and additional strengths into PSGs prior to a petitioned ANDA being approved

ODT: orally disintegrating tablet

Suitability Petition (Tablet -> ODT)

Primidone ODT: Two options

- Two BE studies using the designated RS for primidone tablets
  - Conduct the study by testing one primidone ODT of the test drug product, administered with and without water, compared to one primidone tablet of the RS with water

- One BE study using the designated RS for primidone ODTs
  - Conduct the study by testing one primidone ODT of the test product, administered without water compared to one primidone ODT of the RS without water

Acid Reducing Agent - Detailed Study Design Instructions

PSG Example: Dasatinib

Dasatinib, a BCS low solubility drug with pH-dependent solubility, is formulated to minimize pH-dependent absorption. Therefore, a fasting BE study in presence of an acid-reducing agent is also recommended

- A proton pump inhibitor (PPI, e.g., rabeprazole) is recommended for the selection of acid-reducing agents to compare gastric pH-dependent PK the test product and RLD
- The elevating effect of a proton pump inhibitor on gastric pH (e.g., mean pH over 24 hours, percentage of the time when the pH ≥4.0 in a 24-hour interval) is dependent on the individual PPI and its dose
- Select a PPI that has minimal effect on PK of dasatinib via other interacting mechanisms and a dose that is expected to provide a near maximum effect on gastric acid suppression (i.e., pH elevation)
- Subjects should be pre-treated with a PPI for several days (e.g., 4 to 5 days) to reach its PD steady-state before administering the test product or RLD

PPI: proton pump inhibitor; RLD: reference listed drug; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_216099.pdf

Cross-Referencing Approaches

PSG for Bupropion HCl ER tablets:

- *Bupropion HCl ER tablet (NDA 020711), 150 mg, and bupropion HCl ER tablet (NDA 020358), 100 mg, 150 mg and 200 mg are the subject of two separate RLDs*
- *A waiver of in vivo BE testing for the 150 mg strength using bupropion HCl ER tablet (NDA 020711) as RLD may be requested provided the applicant*
  - *(1) submits an ANDA containing acceptable in vivo studies on the 200 mg strength using bupropion HCl ER tablet (NDA 020358) as RLD;*
  - *(2) cross-references the ANDA for the 150 mg strength using bupropion HCl ER tablet (NDA 020358) as RLD; and*
  - *(3) meets the criteria of 21 CFR §320.24(b)(6)*

ER: extended release; NDA: new drug application; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020358.pdf

Cross-reference BE Studies in Approved Applications

- Applicants may cross reference BE studies in approved applications for a co-packaged product
- Reduces burden of performing additional BE study (studies)
- Examples: PSGs for oral contraceptives
  - *Note that ethinyl estradiol and norethindrone tablets, 0.035 mg; 1 mg and 0.035 mg; 0. 5 mg, 0.035 mg; 0.75 mg, and 0.035 mg; 1 mg are the subject of two separate RLDs.*
  - *Two separate ANDAs must be submitted comparing to the appropriate RLDs. An applicant may request a waiver of in vivo BE testing for generic of these RLDs provided that it*
    - *(1) submits an ANDA containing acceptable BE study on the 0.035 mg; 1 mg strength;*
    - *(2) cross-references the ANDA for the 0.035 mg; 1 mg strength; and*
    - *(3) meets the criteria of 21 CFR § 320.22(d)(2)*
    - *Refer to the most recent version of the FDA guidance for industry on Variations in Drug Products that May Be Included in a Single ANDA*

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_217660.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_017735.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_017576.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_021490.pdf

Study Design – PK sampling

Transparency and Clarity

- Include explanation as to why certain recommendations are made
  - Ensure adequate blood sampling scheme to characterize PK
  - Consideration of where drug is to be released

Budesonide DR Capsule PSG

- intended to primarily release in the ileum, a target site of inflammatory reactions related to progression of primary immunoglobulin A nephropathy
- BE studies: At least four non-zero measurements of concentration for $\mathrm{AUC}_{4-\mathrm{t}}$
  - Sampling points adequately distributed across the time interval to ensure accurate characterization of the concentration-time profile
- At least 4 measurements for $\mathrm{AUC}_{4-\mathrm{t}}$
  - Sampling timepoints adequately distributed across the 0-4 hr interval to accurately characterize the early concentration-time profile and detect any premature drug release

DR: delayed release; AUC: area under the curve; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_215935-REV-2025-12.pdf;

Oral Narrow Therapeutic Index Drugs

FDA publishes PSGs identifying which drugs demonstrate the characteristics of NTI drugs and outlining BE recommendations for these drugs

- PSGs: FDA has concluded that Drug X is an NTI drug based on the following evidence:
  - Range between the effective concentrations and the concentrations associated with serious toxicity is narrow
  - Sub-optimal concentrations lead to severe therapeutic failure or toxicity
  - Subject to therapeutic drug monitoring based on PK or PD measures
  - Exhibits low-to-moderate within-subject variability
  - Dose adjustments are in small increments (<20%)

Oral NTI Drug PSGs:

- Carbamazepine (tablet, ER tablet and capsule, suspension, chewable tablet)
- Cyclosporine (capsule)
- Digoxin (tablet)
- Divalproex sodium (DR tablet, DR capsule/pellets, ER tablet)
- Everolimus (tablet)
- Levothyroxine sodium (tablet, capsule)
- Liothyronine sodium (tablet)
- Lithium carbonate (tablet, capsule, ER tablet)
- Phenytoin/Phenytoin sodium (chewable tablet, suspension, ER capsule)
- Sirolimus (tablet)
- Tacrolimus (capsule, suspension, ER tablet, ER capsule)
- Theophylline (ER tablet, ER capsule)
- Valproic acid (capsule)
- Warfarin (tablet)

PD: pharmacodynamic; Product-Specific Guidances for Generic Drug Development; Donnelly M et al (2025), Clin Pharmacol Ther, 117:116-129

Summary

- FDA has updated published PSGs for oral drug products by incorporating the latest current thinking as new information becomes available, including the BCS-based biowaiver options and M13A recommendations
  - Reduced the burden of conducting additional BE studies for non-high-risk IR products

- FDA's proactive approaches in BE recommendations, such as including suitability petitioned different dosage forms and strengths, cross-referencing BE studies in approved applications, and NTI drugs into PSGs of oral drug products

- Clear and transparent communications with prospective applicants via PSGs by incorporating the rationale for recommendations