Non-Complex Drug Products and Product-Specific Guidances

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SBIA Webinar:
FDA Product-Specific Guidances: Lighting the Development Pathway for Generic Drugs

Learning Objectives

- Discuss non-complex drug products and GDUFA II commitments of non-complex new chemical entities (NCEs)
- Describe format and content of product-specific guidances (PSGs) of non-complex drug products
- Discuss general framework of how PSGs of non-complex drug products are developed and revised
- Share a recent example of significant PSG revisions

Non-Complex Generic Drug Products

- Non-complex drugs:
  - Do not have a complex active ingredient, complex formulation, complex route of delivery, or complex drug device combinations

- FDA to issue PSGs for 90% of non-complex NCEs
  - approved on or after October 1, 2017
  - at least 2 years prior to the earliest lawful ANDA filing date

https://www.fda.gov/media/101052/download; ANDA - abbreviated new drug application

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ceritinib

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Ceritinib

Dosage Form; Route: Tablet; oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 150 mg
   Subjects: Males and females, general population
   Additional comments: Exclude females of reproductive potential and subjects with risk factors for prolonged QTc interval and Torsades de Pointes. Monitor subjects during the study for electrocardiogram changes. Based on the potential for genotoxicity, males with female partners of reproductive potential should be advised to use effective contraception during the study and for 3 months following completion of the study. Subjects should be evaluated before enrollment to ensure normal transaminase (ALT, AST), alkaline phosphatase, and total bilirubin levels. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of ceritinib. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 150 mg
   Subjects: Males, and females of non-reproductive potential, general population
   Additional comments: See comments above.

Analyte to measure: Ceritinib in plasma

Bioequivalence based on (90% CI): Ceritinib

Waiver request of in vivo testing: Not applicable

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, http://www.accessdata.fda.gov/scripts/cder/dissolution/. Conduct comparative dissolution testing

Recommended Nov 2020

Category
Active ingredient
Dosage form and route
Recommended studies
Analyte(s) to measure in appropriate biological fluid
Bioequivalence assessment
Waiver request of in vivo testing
Dissolution test method and sampling time

PSG Content

Category	Examples
Subjects	Healthy subjects, general population, patients, exclude certain specific population (e.g., geriatric, females of reproductive potential)
Design	Single-dose, multiple-dose, crossover, parallel, partial or fully replicate
Type of BE study	Fasting, fed, fasting sprinkle
Analyte(s) to measure, biological matrix	Parent, active metabolite, or both in plasma, serum, whole blood, or urine
Dissolution methods	FDA database, split tablets if appropriate
Waiver	For additional strength(s), BCS 1 or 3
Special considerations	Alcohol dose-dumping, enteral feeding tube, drugs with partial AUC evaluation, NTI drugs, highly variable drugs, endogenous compounds, concomitant drugs, pharmacogenomic information, safety measurements, etc.

BE - bioequivalence; BCS - biopharmaceutical classification system; AUC - area under the curve; NTI - narrow therapeutic index

General Frameworks

- PSGs and FDA Guidance - BE Studies with PK Endpoints for Drugs Submitted under an ANDA
- Current RLD labeling (appropriate subject screening and selection, inclusion and exclusion criteria, study design and conduct, appropriate clinical safety monitoring)
- RLD labeling updates – approval of a new strength, sprinkle on soft food, etc.
- FDA Dissolution Methods Database; FDA Guidances - Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation; Waiver of In Vivo BA and BE Studies for IR Solid Oral Dosage Forms Based on a BCS, M9 BCS-based biowaivers

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https://www.fda.gov/media/87219/download; https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm?event=Home.Letter&searchLetter=I ; http://www.accessdata.fda.gov/scripts/cder/dissolution/; https://www.fda.gov/media/70963/download; https://www.fda.gov/media/117974/download; PK – pharmacokinetic; BE – bioequivalence; RLD – reference listed drug; BA – bioavailability; IR – immediate-release; BCS – Biopharmaceutics Classification System

Valuable Information in PSGs (1)

- BE study design:
  - Drugs with a long elimination half-life – adequate washout period if a crossover design is considered or utilize a parallel study design
  - Analytical assay sensitivity – use of multiple units
- Study subjects
  - Patients -> healthy subjects
  - Exclude specific populations – safety or PK variability related concerns
    - e.g., geriatric subjects, subjects with a certain polymorphic enzyme deficiency (e.g., CYP2C9*3)
  - Use of effective contraception

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_209884.pdf; BE: bioequivalence; PK: pharmacokinetics

Valuable Information in PSGs (2)

- Granules and sprinkle
  - Mix in applesauce or into a certain beverage in accordance with the RLD labeling
- Co-administration of other drugs
  - Use of contraceptives – prevention of pregnancy
- Endogenous drug substances
  - Baseline characterization and correction
  - Enroll study subjects with low baseline endogenous substance concentration to determine the effect of the test and reference products after baseline-correction

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020675.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_213491.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_208010.pdf

Valuable Information in PSGs (3)

- Fed BE study
  - In general, fed BE studies should be conducted with a high-fat meal
  - A fed BE study with a low-fat meal with ~25% of total calories from fat in lieu of a high fat BE study if serious adverse events are anticipated under fed conditions
    - Additional comments section in PSGs
- Co-packaged products
  - If an ANDA applicant has an approved ANDA for the single entity of a co-packaged product, the applicant may cross reference its approved ANDA for this co-packaged product

Valuable Information in PSGs (4)

- Highly variable drug (HVD) information in PSGs
  - Applicants may use three-period or four-period reference-scaled average BE approach for HVDs
  - Applicants should provide evidence of high variability in the BE parameters of AUC and/or C_{max} (i.e., intrasubject variability ≥ 30%)

Valuable Information in PSGs (5)

- Biopharmaceutics Classification System (BCS) information in PSGs
  - There are many drugs with high solubility potentially eligible for BCS waiver
  - FDA adds BCS waiver recommendation to PSGs when the FDA BCS Committee has reached agreement on the classification
  - BCS Waiver Option not in PSGs:
    - FDA may not have classified them
    - BCS waiver can be requested by submitting a controlled correspondence with data and substantive questions (e.g., when approaches are deviated from BCS guidance)
    - Refer to the FDA Guidances, Waiver of In Vivo BA and BE Studies for IR Solid Oral Dosage Forms Based on a BCS, M9 BCS-based biowaivers
    - May use information contained in the approved labeling of the reference product for the purpose of establishing high permeability of the drug substance

https://www.fda.gov/media/70963/download; https://www.fda.gov/media/117974/download

Revisions – PSGs (Fed/Fasting)

- Increased transparency on PSGs gives applicants a better opportunity to efficiently allocate resources
- However, some PSGs were not in alignment with FDA's current thinking on fed/fasting BE studies for orally administered drug products
- As a result, ANDA applicants were asked for a fed study as part of the ANDA assessment
- Reliability of some PSGs in question
- A recently completed major effort in PSG revision: fed/fasting BE studies
- Better to know the current advice in PSGs rather than waiting for an ANDA deficiency

Summary

- PSGs and general BE guidance provide scientific recommendations to efficiently develop generic drug products
- FDA continues to meet the GDUFA II commitment (100%):
  - FDA to issue PSGs for 90% of non-complex NCEs approved on or after Oct 1, 2017, at least 2 years prior to the earliest lawful ANDA submission date
- Prioritized FDA's ongoing efforts to update PSGs with the latest current thinking as new information becomes available
- Applicants may use an alternative approach to establish BE

Resources

- PSGs for Generic Drug Development: https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm
- FDA Draft Guidance for Industry, BE Studies with PK Endpoints for Drugs Submitted Under an ANDA: https://www.fda.gov/media/87219/download
- FDA Guidance for Industry on Waiver of In Vivo BA and BE studies for IR Solid Oral Dosage Forms Based on a BCS: https://www.fda.gov/media/70963/download
- M9 BCS-based biowaivers: https://www.fda.gov/media/117974/download
- FDA-Recommended Dissolution Methods: https://www.accessdata.fda.gov/scripts/cder/dissolution/
- FDA Guidance for Industry on Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation: https://www.fda.gov/media/81626/download


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