Product-Specific Guidance Fundamentals from a Clinical Perspective

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

Outline

- Study Population and Terminology
- Bioequivalence Studies with Pharmacokinetic Endpoints
- Bioequivalence Studies with Comparative Clinical Endpoint(s)
- Mandatory Safety Reporting and Other Clinical Considerations

Study Population and Terminology

Study Population

- Healthy subjects/general population unless otherwise recommended
- Age 18 years or older
- If intended for both sexes include similar proportions males and females
- Females should be non-lactating, non-pregnant and if applicable, practice abstention or contraception

Terminology

- **Healthy subjects:** non-smoking, no existing medical conditions or medications
- **General population:** broad collection of adults, may have stable chronic conditions and may be treated with therapeutics that will not interfere with study drug or bio-assay
- **Patients:** study drug is indicated for them based on diagnosed condition

Terminology (cont.)

- **Non-lactating, non-pregnant:** not breast feeding or expressing human milk and have negative pregnancy tests
- **Females not of reproductive potential:** post-menopausal or post-hysterectomy
- **Female Subjects Using Effective Contraception:** permanent sterilization, intrauterine device or progesterone implant, or combination hormonal contraceptive plus barrier method

Bioequivalence (BE) Studies with Pharmacokinetic (PK) Endpoints

Additional comments: Exclude subjects with abnormal liver function tests and with risk factors for prolonged QTc interval and Torsades de Pointes. Subjects should be appropriately monitored for electrocardiogram changes during the study. Females of reproductive potential should use effective contraception during the study and for 5 weeks following the final dose of entrectinib. Males with female partners of reproductive potential should use effective contraception during the study and for 3 months following the final dose of entrectinib.

Subj

Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: Exclude subjects with abnormal liver function tests and with risk factors for prolonged QTc interval and Torsades de Pointes. Subjects should be appropriately monitored for electrocardiogram changes during the study. Females of reproductive potential should use effective contraception during the study and for 5 weeks following the final dose of entrectinib. Males with female partners of reproductive potential should use effective contraception during the study and for 3 months following the final dose of entrectinib.

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2. Type of study: Fed
Design: Single-dose, two-treatment, two-period crossover in vivo
Strength: 200 mg
Subjects: Males and non-pregnant, non-lactating females, general population
Additional comments: See comments above

Analyte to measure: Entrectinib in plasma

Bioequivalence based on (90% CI): Entrectinib

Waiver request of in vivo testing: 100 mg based on (i) acceptable bioequivalence studies on the 200 mg strength, (ii) proportional similarity of the formulations between both strengths, and (iii) acceptable in vitro dissolution testing of both strengths

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

BE Studies With PK Endpoints

- Generally, two studies, fed and fasting
  - Immediate-release product may omit fed if reference listed drug (RLD) states to be taken on empty stomach
  - Modified-release product fed and fasting irrespective of RLD dosing instructions
  - May omit fed or fasting study if serious adverse events anticipated in fed or fasting state

BE Studies With PK Endpoints (cont.)

- Design generally, two-period, two-sequence, two-treatment, single-dose, crossover, or a replicate study design
  - May use single-dose, parallel design for long half-lives (i.e., longer than 24 hours)
  - Generally conducted on the highest strength unless safety considerations preclude its use
  - If an applicant does not intend to submit an ANDA for the highest strength of the reference product – as recommended in the PSG – then generally, should use the highest strength included in the ANDA
  - Healthy subjects/general population unless otherwise recommended

BE Studies With PK Endpoints (cont.)

- Additional Comments Section
  - Drug-specific recommendations that often will be related to key safety issues to be considered
  - Frequent comments related to cardiac electrophysiology, testing for predisposition to organotoxicities prior to enrollment, post-dose monitoring
  - Additionally, recommendations related to male/female contraception during and after study

BE Studies with Comparative Clinical Endpoint(s)

Contains Nonbinding Recommendations

Draft – Not for Implementation

Draft Guidance on Ferric Maltol

March 2021

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: Ferric maltol

Dosage Form; Route: Capsule; oral

Recommended Studies: Two options

I. Option 1:

II. Option 2:

If the test product formulation is not Q1/Q2 the same as the RLD with respect to excipients, bioequivalence should be established by conducting an in vivo bioequivalence study with clinical endpoints and in vitro dissolution testing.

Recommended studies: Bioequivalence study and in vitro dissolution testing

1. Type of study: Bioequivalence study with clinical endpoint
   Design: Randomized, double blind, parallel, three arm, placebo-controlled in vivo
   Strength: 30 mg iron
   Subjects: Males and non-pregnant, non-lactating females, with quiescent inflammatory bowel disease and iron deficiency anemia
   Additional comments: Specific recommendations are provided below.

2. Type of study: In vitro comparative multi-media dissolution studies
   The same studies as recommended under Option 1.

BE Studies with Comparative Clinical Endpoint(s)

- Additional Comments Section
  - Enrollment criteria
  - Recommended endpoints
  - Examples of prohibited meds
  - Approach to statistical analysis
  - Suggested headings for dataset submission

BE Studies with Comparative Clinical Endpoint(s) (cont.)

- For more recently published guidances
  - The approach to statistical analysis can be found in an index guidance
    - The product-specific guidance on adapalene; benzoyl peroxide topical gel, 0.3%; 2.5% entitled Guidance on Adapalene; Benzoyl Peroxide
  - There is a link to the Study Data Standards Resource webpage that includes required items and helpful tools for submission of study data

BE Studies with Comparative Clinical Endpoint(s) (cont.)

- A technical guide for comparative clinical endpoint bioequivalence studies is also on the Study Data Standards Resource webpage

- The guide provides recommended technical specifications and general considerations on how certain comparative clinical endpoint bioequivalence study data and skin adhesion and irritation/sensitization (I/S) study data for ANDAs should be submitted using FDA-supported data standards located in the FDA Data Standards Catalog

BE Studies with Comparative Clinical Endpoint(s) (cont.)

- Along with I/S studies, the guide should be used for adhesion studies and comparative clinical studies using primary endpoints based on:
  - Inflammatory and/or non-inflammatory lesion counts
  - 100% clearance of all actinic keratosis lesions
  - Treatment Success Based on Physician's Global Assessment (PGA) and Psoriasis Area Severity Index (PASI)
  - Total Nasal Symptom Score
  - Intraocular pressure for both eyes
  - Therapeutic cure

BE Studies with Comparative Clinical Endpoint(s) (cont.)

- Within a PSG there may be reference to general guidances
- General guidances contain overarching principles that are relevant to PSGs related to a specific product class
- Examples
  - Transdermal and topical delivery systems
    - Draft guidance *Assessing the Irritation and Sensitization Potential of Transdermal and Topical Delivery Systems for ANDAs* (October 2018)
    - Draft guidance *Assessing Adhesion With Transdermal and Topical Delivery Systems for ANDAs* (October 2018)

BE Studies with Comparative Clinical Endpoint(s) (cont.)

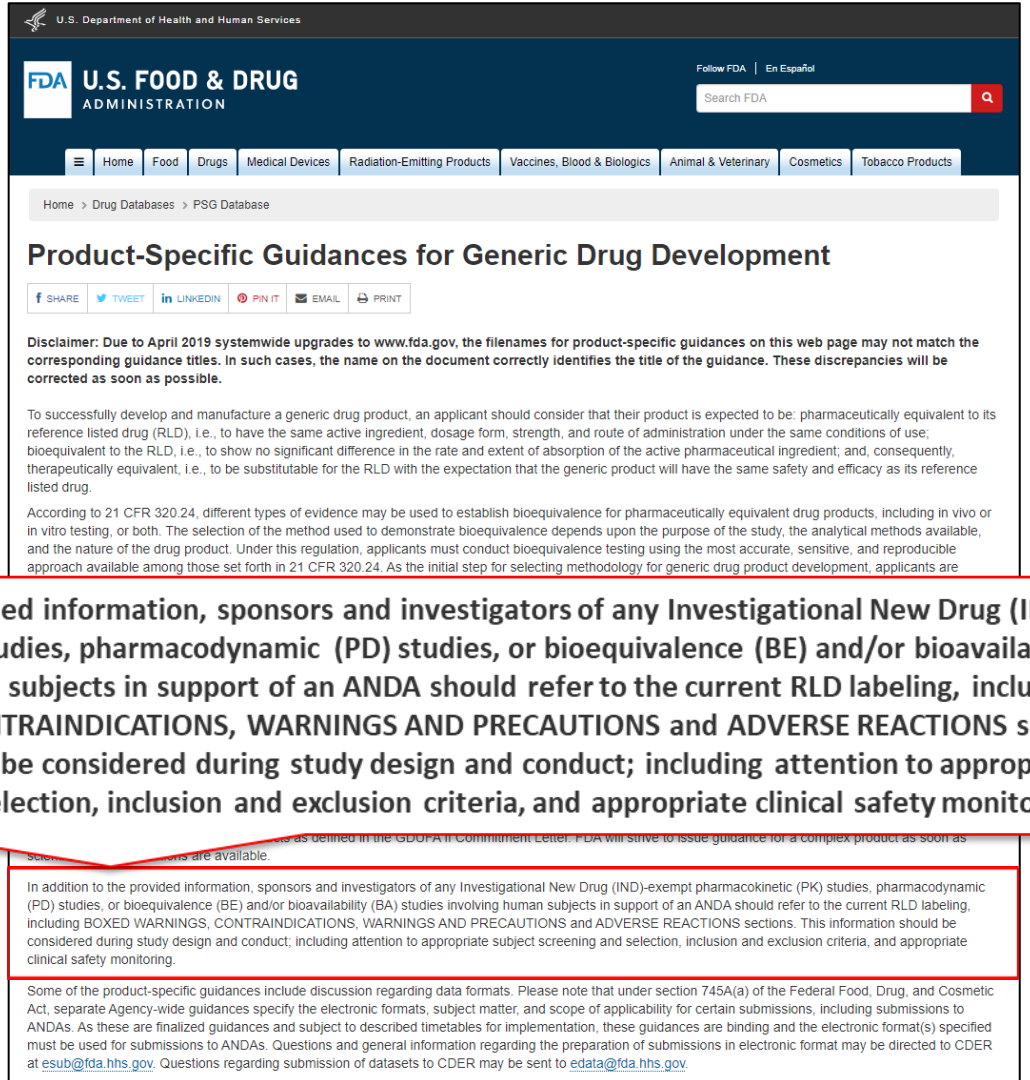
- Examples (cont.)
  - Opioids with abuse deterrent formulation
    - Draft guidance *General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products* (March 2016)

Mandatory Safety Reporting and Other Clinical Considerations

Mandatory Safety Reporting – 21 CFR 320.31(d)(3)

- The person conducting the study, including any contract research organization, must notify FDA and all participating investigators of any serious adverse event, as defined in §312.32(a), observed during the conduct of the study as soon as possible but in no case later than 15 calendar days after becoming aware of its occurrence
- Each report must bear prominent identification of its contents, i.e., "bioavailability/bioequivalence safety report"
- The person conducting the study, including any contract research organization, must also notify FDA of any fatal or life-threatening adverse event from the study as soon as possible but in no case later than 7 calendar days after becoming aware of its occurrence
- Each notification under this paragraph must be submitted to the Director, Office of Generic Drugs in the Center for Drug Evaluation and Research at FDA. Relevant follow-up information to a bioavailability/bioequivalence safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Followup bioavailability/bioequivalence safety report."

Other Safety Considerations



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Product-Specific Guidances for Generic Drug Development

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Disclaimer: Due to April 2019 systemwide upgrades to www.fda.gov, the filenames for product-specific guidances on this web page may not match the corresponding guidance titles. In such cases, the name on the document correctly identifies the title of the guidance. These discrepancies will be corrected as soon as possible.

To successfully develop and manufacture a generic drug product, an applicant should consider that their product is expected to be: pharmaceutically equivalent to its reference listed drug (RLD), i.e., to have the same active ingredient, dosage form, strength, and route of administration under the same conditions of use; bioequivalent to the RLD, i.e., to show no significant difference in the rate and extent of absorption of the active pharmaceutical ingredient; and, consequently, therapeutically equivalent, i.e., to be substitutable for the RLD with the expectation that the generic product will have the same safety and efficacy as its reference listed drug.

According to 21 CFR 320.24, different types of evidence may be used to establish bioequivalence for pharmaceutically equivalent drug products, including in vivo or in vitro testing, or both. The selection of the method used to demonstrate bioequivalence depends upon the purpose of the study, the analytical methods available, and the nature of the drug product. Under this regulation, applicants must conduct bioequivalence testing using the most accurate, sensitive, and reproducible approach available among those set forth in 21 CFR 320.24. As the initial step for selecting methodology for generic drug product development, applicants are

In addition to the provided information, sponsors and investigators of any Investigational New Drug (IND)-exempt pharmacokinetic (PK) studies, pharmacodynamic (PD) studies, or bioequivalence (BE) and/or bioavailability (BA) studies involving human subjects in support of an ANDA should refer to the current RLD labeling, including BOXED WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS sections. This information should be considered during study design and conduct; including attention to appropriate subject screening and selection, inclusion and exclusion criteria, and appropriate clinical safety monitoring.

as defined in the GDUFA II Commitment Letter. FDA will strive to issue guidance for a complex product as soon as scientific considerations are available.

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Some of the product-specific guidances include discussion regarding data formats. Please note that under section 745A(a) of the Federal Food, Drug, and Cosmetic Act, separate Agency-wide guidances specify the electronic formats, subject matter, and scope of applicability for certain submissions, including submissions to ANDAs. As these are finalized guidances and subject to described timetables for implementation, these guidances are binding and the electronic format(s) specified must be used for submissions to ANDAs. Questions and general information regarding the preparation of submissions in electronic format may be directed to CDER at esub@fda.hhs.gov. Questions regarding submission of datasets to CDER may be sent to edata@fda.hhs.gov.

Other Safety Considerations (cont.)

- Requirements for Investigational New Drug Application (Bio-IND) – 21 CFR 320.31
  - Radioactively labeled or cytotoxic
  - Single-dose study where either the maximum single or total daily dose exceeds that specified in the labeling
  - Multiple-dose study where either the single or total daily dose exceeds that specified in the labeling
  - Multiple-dose study on an extended-release product on which no single-dose study has been completed

Questions?

Closing Thought

Adherence to the principles of good clinical practice, including human subject protection, is universally recognized as a critical requirement to the ethical conduct of research involving human subjects*

*FDA website *Clinical Trials and Human Subject Protection*


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