Bioequivalence Approaches for Generic Drug Product Development and Approval in the United States

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ABSTRACT

Purpose: The Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)) requires that an applicant submitting an abbreviated new drug application (ANDA) to the U.S. Food and Drug Administration (FDA) for marketing approval of a new generic drug product must show that the generic product is, among other things, "bioequivalent" to the corresponding reference listed drug (RLD). Bioequivalence is defined under 21 CFR § 314.3(b) as "the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study." The purpose of the present study is to provide an overview of the current bioequivalence approaches and standards used in generic drug product development and regulatory approval in the United States.

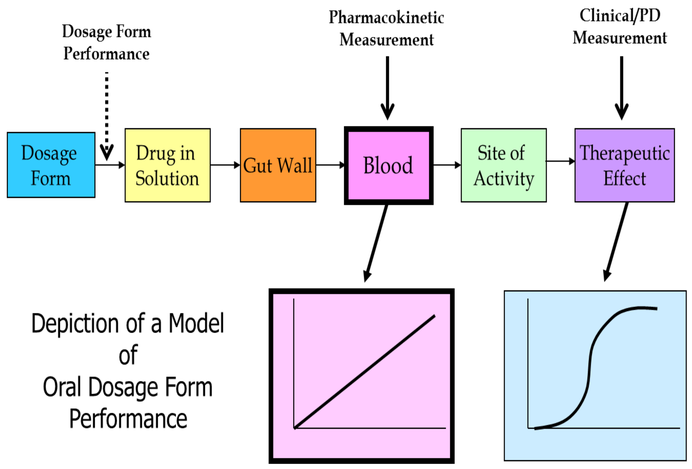
Methods: The bioequivalence approaches and standards used to support development and approval of generic drug products with various dosage forms were examined and summarized.

Results: Various dosage form products include immediate-release and modified-release (including delayed-release and extended-release) oral dosage form drugs, which can act systemically and/or locally. In addition, there are drug products with various dosage forms dosed via different routes of administration, for example, via oral (e.g., chewable, sublingual, buccal, orally disintegrating), transmucosal/oral (e.g., gum, troche/lozenge), intravenous infusion (e.g., injection, liposome), subcutaneous (e.g., injection, implant), intramuscular (e.g., injection, injectable depot, suspension), intrauterine/intralymphatic (e.g., injection), topical dermatological (e.g., ointment, gel, cream, lotion, foam/aerosol, solution, swab, shampoo/suspension, spray, powder, film), transdermal (e.g., film, gel/metered, gel, solution/metered), nasal/inhalation (e.g., solution, powder, metered aerosol, metered spray), ophthalmic (e.g., solution/drops, suspension/drops, ointment, emulsion), vaginal (e.g., insert, tablet, cream, gel, ring, suppository), rectal (e.g., aerosol/metered, suppository), dental (e.g., paste), enteral (e.g., suspension), urethral (e.g., suppository), and etc. Different bioequivalence approaches and standards for developing and approving generic drug products are recommended by FDA* to industry by considering many factors, such as dosage form, indication, route of drug administration, and physico-chemical properties of the active pharmaceutical ingredient and excipient.

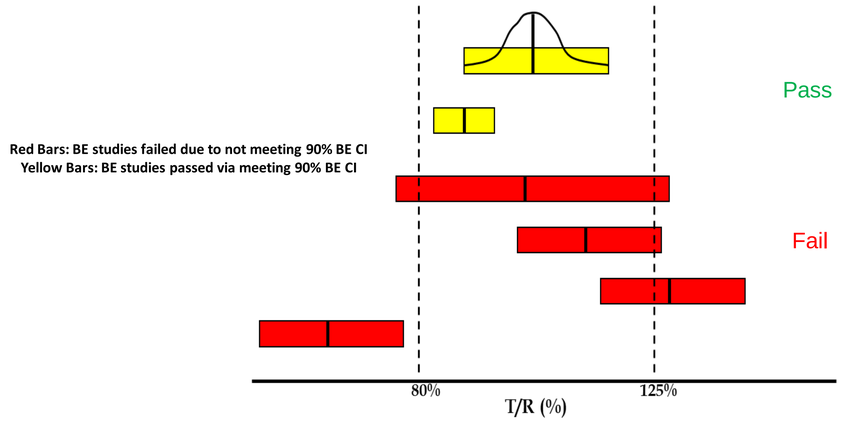
Conclusion: To demonstrate bioequivalence between test (or generic) and reference (or RLD) products, in vivo and/or in vitro bioequivalence approaches have been utilized in generic drug development and approvals. While bioequivalence studies with pharmacokinetic, pharmacodynamic, or comparative clinical endpoints are the most common in vivo bioequivalence approaches, in vitro bioequivalence approaches, composed of in vitro equilibrium binding, in vitro kinetic binding, in vitro microbial kill rate study, battery tests for nasal and inhalation products, microscopic birefringence test, time to break test, in vitro feeding tube tests, in vitro permeation test, in vitro release test, and qualitatively/quantitatively/physico-chemical characterization (Q1/Q2/Q3) of inactive ingredients, are also being recommended and employed. FDA's effort in establishing innovative, valid, and sensitive bioequivalence approaches and standards for generic drug product development and approval has promoted safe, effective, high quality, and affordable generic medicines available to all American consumers. Generic drug products have saved a total of $293 billion in healthcare costs for prescriptions dispensed in 2018 in the United States.

RESULTS

In Vivo Bioequivalence Approaches for Systemically-Acting Oral Solid Dosage Forms



In Vivo Pharmacokinetic Bioequivalence Studies Bioequivalence Criteria {90% Confidential Interval (CI)}



In Vivo Bioequivalence Approaches → Pharmacokinetic Study; Comparative Clinical Endpoint Study; Pharmacodynamic Endpoint Study

In Vitro Bioequivalence Approaches → In Vitro Equilibrium Binding; In Vitro Kinetic Binding; In Vitro Microbial Kill Rate Study; Battery Test for nasal/inhalation products; Microscopic Birefringence Analysis; Time to Break Analysis; In Vitro Feeding Tube Tests; In Vitro Permeation Test; Q1/Q2/Q3

Disclaimer: "The views expressed in this poster are those of the author and do not necessarily represent FDA's views or policy."

RESULTS

Bioequivalence Approaches for Drugs in Various Dosage Form

Bioequivalence Approaches for Systemically-Acting Drug Products → Intended to be delivered to sites of action in the body via the bloodstream → *Pharmacokinetic Study by measuring drug and/or metabolite concentrations in the biological matrix

Bioequivalence Approaches for Locally-Acting Drug Products → *Not intended to be delivered to sites of action in the body via the bloodstream; *Systemic absorption may not be measurable; *Absorption may be highly variable → *Comparative Clinical Endpoint Study; Pharmacodynamic Endpoint Study; *Alternative In Vitro BE approach: Q1/Q2/Q3

OUTCOMES

Source: Regulatory Focus. FDA Sets Record for Number of Generic Drug Approvals Again. Published on Oct. 11, 2018.

Note: The FDA generic drugs approvals for FY 2019 are 934. Among them, 63.5% of approvals is for oral solid dosage form. Also, there are 237 tentative approvals pending with FDA.

CONCLUSIONS

To demonstrate bioequivalence between test (or generic) and reference (or RLD) products, both in vivo and/or in vitro bioequivalence approaches have been utilized to promote the generic drug development and approvals.

*FDA's Product-Specific Guidances for Generic Drug Development Website is located at https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm.