M0930-04-24

DEVELOPING EFFICIENT BIOEQUIVALENCE APPROACHES FOR GENERIC VAGINAL DRUG PRODUCTS

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PURPOSE

The development of generic vaginal drug products has historically involved in vivo bioequivalence (BE) studies with pharmacokinetic endpoints and/or clinical endpoint(s). In recent years, the Office of Generic Drugs (OGD) at the U.S. Food and Drug Administration (FDA) has begun recommending efficient characterization-based approaches for generic topical drug products applied to the skin within product-specific guidances (PSGs). The components that are recommended as part of a characterization-based approach often depend on the complexity of the product (e.g., dosage form) and the site/mechanism of action of the drug product. Using a similar framework, efficient characterization-based approaches that may mitigate the risks associated with potential failure modes for BE have been proposed for generic vaginal drug products.

OBJECTIVES

The purpose of this work is to assess BE approaches recommended for developing generic vaginal drug products and to consider research that can support the development of efficient BE recommendations for such products.

METHODS

The total number of products for which PSGs have been developed by FDA was obtained from the FDA's Orange Book (current through July 2022) by filtering the list of approved drug products by route of administration (vaginal) and market status (prescription or over the counter). Orange Book listings that contained "extended release" or multiple dosage forms (e.g., cream and suppository) were excluded from the analysis. Through Generic Drug User Fee Amendments (GDUFA)-funded research, the potential failure modes for BE for such drug products were previously identified. In the current work, PSGs for vaginal semisolid drug products published prior to July 2022 were categorized based on the recommended BE approaches: 1) characterization-based BE approach, 2) comparative clinical endpoint BE study only, 3) comparative clinical endpoint BE study and PK BE study, or 4) no PSG available. PSGs that include multiple BE approaches were classified based on the approach that is listed first in the current PSG page (characterization-based approaches are typically listed first, when a PSG includes multiple approaches). Gap analysis was conducted for vaginal drug products that do not currently include efficient approaches for establishing BE and research needed to address such gaps was identified.

RESULTS

❖ *Current PSG recommendations*

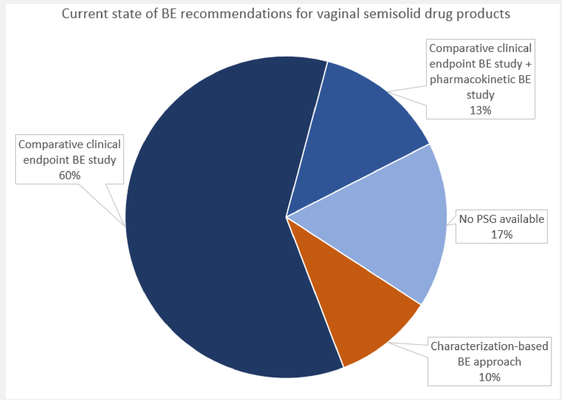

Figure 1. Current state of BE recommendations for vaginal semisolid drug products (n= 30 vaginal products). No BE recommendations are currently available for 5 of the 30 vaginal products. The orange section represents efficient approaches for establishing BE; blue sections represent products for which BE recommendations are either less efficient or unavailable.

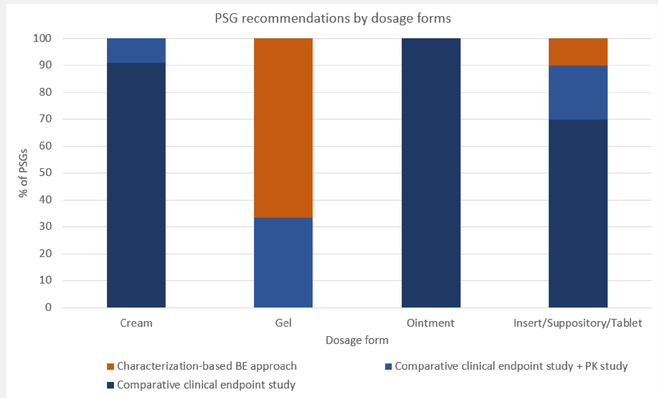

Figure 2. Current BE approaches recommended within posted PSGs for vaginal creams, gels, ointments, and insert/suppository/tablets. The orange section represents efficient approaches for establishing BE; blue sections represent approaches for establishing BE that are considered to be less efficient. Creams, gels and inserts/suppositories/tablets are the most commonly used dosage forms for vaginal semisolid drug products.

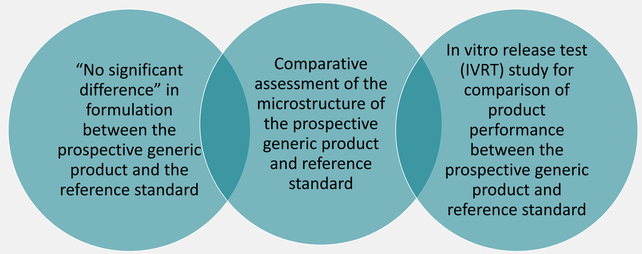

Figure 3. Efficient characterization-based BE approach recommended in PSGs for metronidazole vaginal gel, 0.75% and 1.3%

❖ *Complexity of vaginal dosage forms*

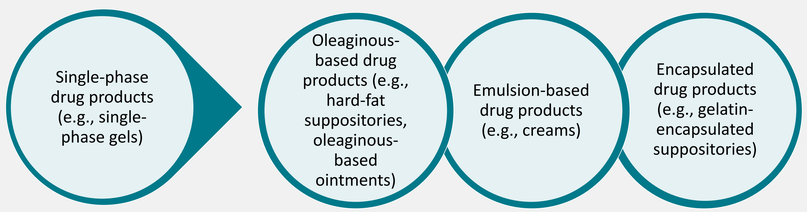

Figure 4. Complexity of vaginal dosage forms that are less complex (left circle) to more complex (right circles). Based on an assessment of the microstructure of vaginal reference products, single-phase gels were determined to be the least complex dosage form of those evaluated. Emulsion-based drug products, such as creams, generally appear to be more complex in microstructure compared to single phase gels, thereby increasing the potential failure modes for BE for such products. Encapsulated drug products where the release of the drug from the dosage form, and thereby bioavailability, may be influenced by the rate of disintegration of a "shell" also contribute to the complexity.

❖ *IVRT for vaginal creams[1,2]*

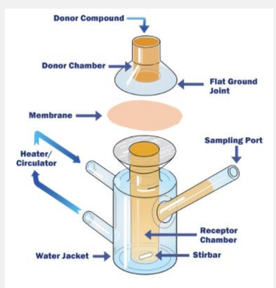

Image from PermeGear website (permegear.com/franz-cells/)

IVRT study conditions

- Apparatus: Vertical Franz diffusion cell (VDC)
- Contact area: 1.77cm^2
- PES membrane (0.45 µm)
- Membrane temperature: 37°C
- Receptor solution: Simulated vaginal fluid containing 3% BrijO20 (pH 4.2)
- Dose : 750 mg vaginal creams

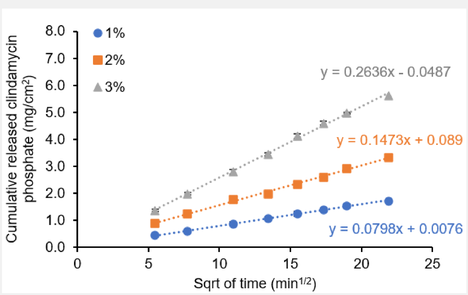

Figure 5. Mean (± SD) in vitro release profiles of three laboratory-made clindamycin phosphate vaginal creams of different nominal strengths (n=3 per strength).

Opportunities with FDA

Looking for a post-doctoral opportunity?
https://www.zintellect.com/Opportunity/Details/FDA-CDER-2022-0791

Looking for funding for generic drug research?
https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

CONCLUSIONS

Efficient characterization-based approaches for vaginal drug products have been developed for single-phase vaginal gels, and previous research has suggested that it may be feasible to develop efficient characterization-based approaches for more complex vaginal drug products, such as emulsions. However, additional research is needed to develop biorelevant performance tests for generic vaginal drug products in order to support development of efficient BE approaches for such products.

FUNDING AND DISCLAIMERS

[1]This project is supported by the Food and Drug Administration (FDA) of the U.S. Department of Health and Human Services (HHS) as part of a grant (U01FD006721) totaling $500,000 with 100 percent funded by FDA/HHS.
[2] A portion of these data (IVRT for vaginal creams) are adapted from work presented at the 2021 AAPS PharmSci360 Meeting in a poster entitled "Development of an In Vitro Release Testing Method for Vaginal Creams" (Yue et al.; Poster number W1030-03-13).
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