Facilitating Drug Development Through GDUFA Regulatory Science and Research Opportunities for Collaboration with FDA

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Purpose

The bioavailability (BA) of the active ingredient from a drug product is typically evaluated using pharmacokinetic studies in which the rate and extent to which a drug becomes available at or near the site of action (in the blood/plasma) is measured. However, for locally acting products in the skin it has been historically challenging to evaluate bioavailability at or near the site of action in the skin, and thereby establish bioequivalence (BE).

The poster provides an overview of the multimillion-dollar research program under the Generic Drug User Fee Amendments (GDUFA) designed to advance the public health by enhancing patient access to safe and effective generic drugs.

Specifically, as it relates to topical drug products applied to the skin, research within the scope of the GDUFA science and research program has supported the development, and implementation of efficient, predominantly in vitro-based approaches, for evaluation of drug product equivalence. The poster will also provide an overview of the cutaneous pharmacokinetic-based approaches (microdialysis/dermal open flow microperfusion, non-invasive quantitative tomography) that are currently being explored within the scope of the program. The poster also discusses the strengths and limitations of individual in vitro methods, and the advantages of combinatorial strategies using evidence from orthogonal assessments.

The ultimate goal is to identify new in vitro, in vivo as well as in silico methodologies that can be utilized to evaluate drug bioavailability at or near the site of action and to discuss how investigators can collaborate with the FDA and access FDA funding opportunities for future research projects via a variety of funding mechanisms.

Useful Links

- Generic Drug Research Priorities & Projects
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-priorities-projects
- Generic Drug Research-Related Guidances & Reports
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-publications-resources
- Generic Drug Research Collaborations and Fellowship Opportunities
  - https://www.fda.gov/drugs/generic-drugs/generic-drug-research-collaboration-opportunities

Collaboration Opportunities

Fellowship

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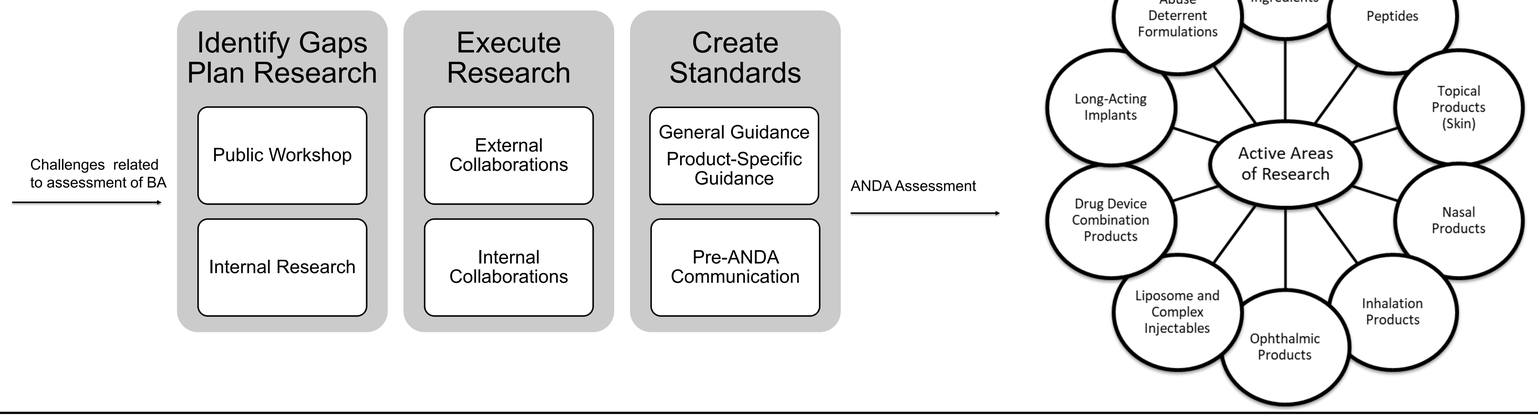
Disclaimer

The views expressed here do not reflect official policies of the US FDA or the Department of Health and Human Services, nor does any mention of trade names imply endorsement by the US Government.

Overview of GDUFA Science and Research program

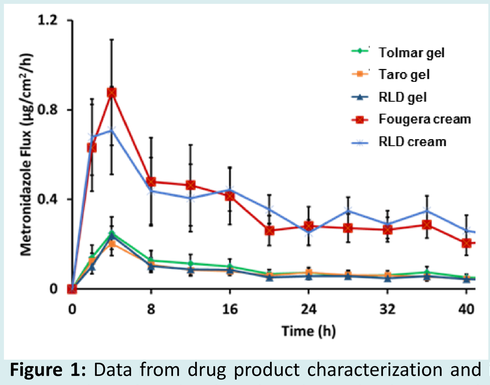


Example: In vitro-based Approaches

Drug Product Characterization

Quality Attribute	MetroCream (RLD)	Generic Cream (Fougera)	Metrogel (RLD)	Generic Gel (Tolmar)	Generic Gel (Taro)
pH	4.8	5.1	5.2	5.0	5.4
Density (g/cc)	1.02	1.02	1.01	1.02	1.02
WOA (g.sec)	57.6	63.9	39.4	43.9	42.0
Particle size (µm)	Active ingredient is completely dissolved				
Drug in Aq (mg/g)	4.20	2.92	---	---	---
Drug in Oil (mg/g)	2.58	3.94	---	---	---
Solvent Activity	0.977	0.974	0.992	0.994	1.002
Globule size, d_{50} (µm)	2.8	2.2	---	---	---
Drying,T_{30}(min)	17	11.4	5.5	4.7	6.5

In Vitro Permeation Test



Current Recommendation Product Specific Guidance

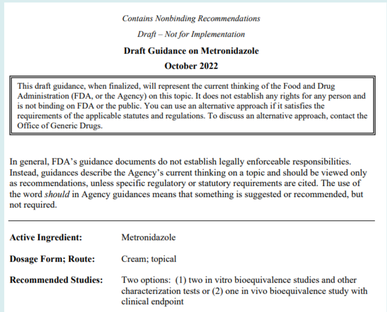

Contains Nonbinding Recommendations
Draft – Not for Implementation
Draft Guidance on Metronidazole
October 2022
This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person 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.
In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.
Active Ingredient: Metronidazole
Dosage Form; Route: Cream; topical
Recommended Studies: Two options: (1) two in vitro bioequivalence studies and other characterization tests or (2) one in vivo bioequivalence study with clinical endpoint

Figure 1: Data from drug product characterization and in vitro evaluation of drug product performance were evaluated to elucidate the relationship between drug product microstructure and performance for a variety of drug products. Data for metronidazole gels and creams shown above (Data courtesy Dr. Narasimha Murthy). The current recommendations for such products are reflected in product-specific guidances for Generic Drug Development https://www.accessdata.fda.gov/scripts/cder/psg/index.cfm

Example: Cutaneous Pharmacokinetic-based Approaches

dermal Open Flow Microperfusion (dOFM)

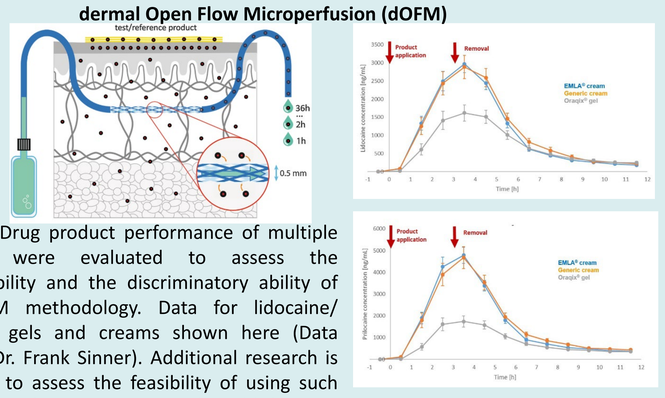
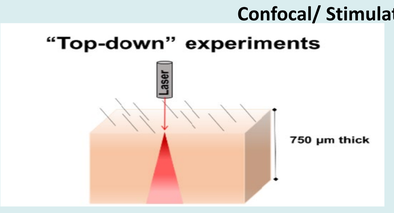


Figure 2: Drug product performance of multiple products were evaluated to assess the reproducibility and the discriminatory ability of the dOFM methodology. Data for lidocaine/ prilocaine gels and creams shown here (Data courtesy Dr. Frank Sinner). Additional research is underway to assess the feasibility of using such methodology for assessing BA and establishing BE

Confocal/ Stimulated Raman Spectroscopy



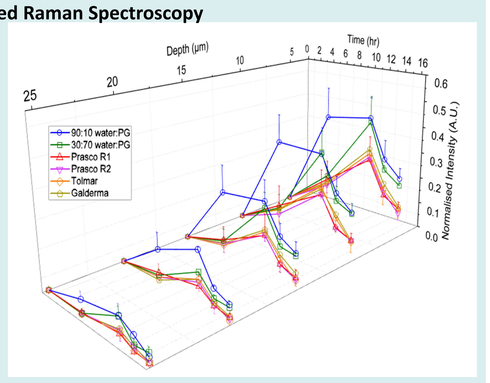
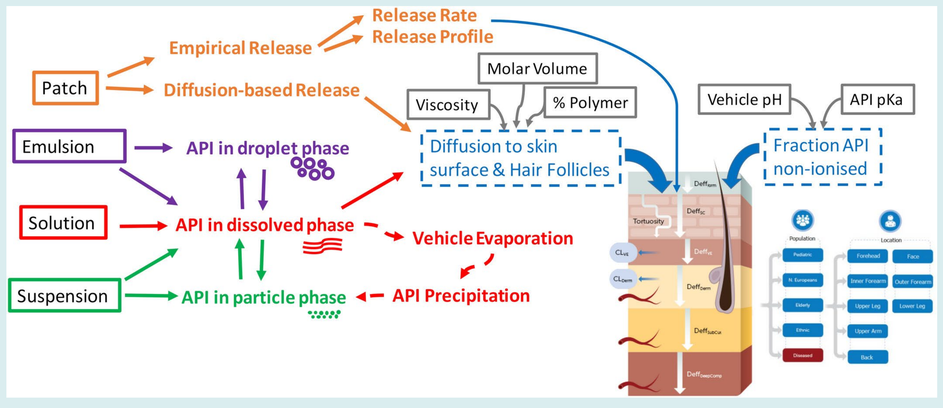


Figure 3: Drug product performance of multiple products were evaluated to assess the reproducibility and the discriminatory ability of confocal and stimulated Raman spectroscopy. Data for metronidazole gels shown here (Data courtesy Prof. Richard Guy). Additional research is underway to assess the feasibility of using such methodology for assessing BA

Example: Combinatorial Strategies



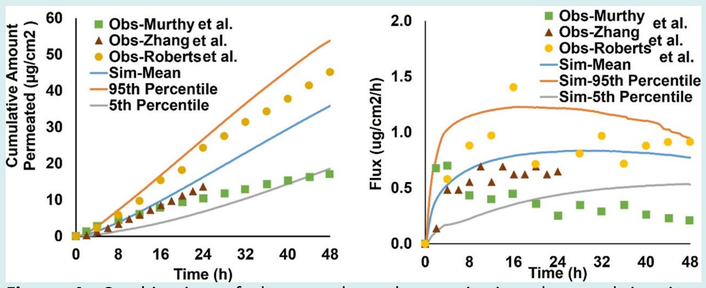


Figure 4: Combination of drug product characterization data and in vitro performance data were systematically used predict the local BA of the active pharmaceutical ingredient at or near the site of action in the skin using a physiologically based pharmacokinetic (PBPK) model. Data for metronidazole gels are cream shown here. Arora et al. Mol Pharm. 2022;19(9):3139-3152. doi:10.1021/acs.molpharmaceut.2c00229