GDUFA Regulatory Science Research on In Vitro Bioequivalence Methods

Darby Kozak, PhD

Division of Therapeutic Performance

Office of Research and Standards, Office of Generic Drugs

CDER, FDA

FY2020 Generic Drug Regulatory Science Initiatives Public Workshop

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Towards In Vitro Bioequivalence (BE)

- Regulatory considerations and GDUFA research
  - Current GDUFA-funded research on in vitro BE approaches
  - Development of Product-Specific Guidances (PSGs)
- Recent successes in generic drug research and approval, as well as identified research needs:
  - Orally Inhaled Drug Products (OIDPs)
  - Parenteral, ophthalmic, and otic drug products
  - Topical dermal, vaginal, and rectal drug products
- Perceived knowledge gaps and research needs to expand in vitro approaches to more complex products

Demonstrating BE

- 21 CFR 320.24 outlines the types of studies that may be used to demonstrate BE:
    1) in vivo pharmacokinetic (PK) studies;
    2) in vivo pharmacodynamic (PD) effect BE studies;
    3) comparative clinical endpoint BE studies; or
    4) in vitro studies.*¥
- Each BE option has inherent benefits, risks, and limitations. Not all options may be appropriate for a proposed generic.
- ***Ultimately, a BE approach must provide an accurate, sensitive, and reproducible measure to ensure bioavailability and BE.***

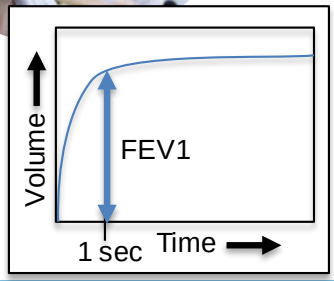
* An in vitro test that has been correlated with and is predictive of human in vivo bioavailability data is considered to be as accurate, sensitive, and reproducible as a comparative in vivo PK study; 21 CFR 320.24(b)(1)(ii)

¥ Or any other approach deemed adequate by FDA to measure bioavailability or establish bioequivalence; 320.24(b)(6)

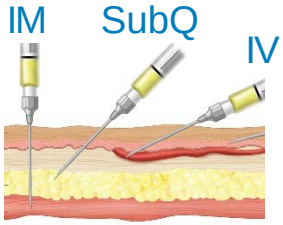
Examples of In Vivo BE Study Challenges

Inhalation

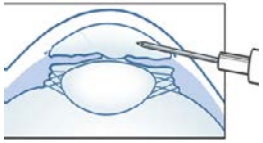
Comparative clinical endpoint BE studies are generally highly variable and less sensitive to formulation and product differences and require a large patient population to statistically power the study.



Parenteral Injectable

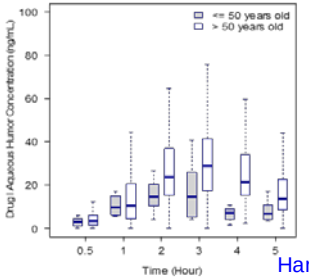


PK studies are typically considered to be most accurate approach to demonstrate BE. However, PK of intravenous (IV) products is less sensitive to formulation differences and it is challenging to recruit and statistically analyze stead-state PK studies of long acting injectables.



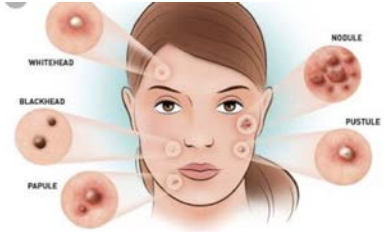
Ophthalmic

Aqueous humor PK is challenging to recruit and statistically power: Sparse sampling as well as effects from subject age and ethnicity give rise to the need for large study population and statistical bootstrapping.



Harigaya, Yoriko, et al. *Pharmaceutical research* 36.1 (2019): 13.

Dermal and Transdermal

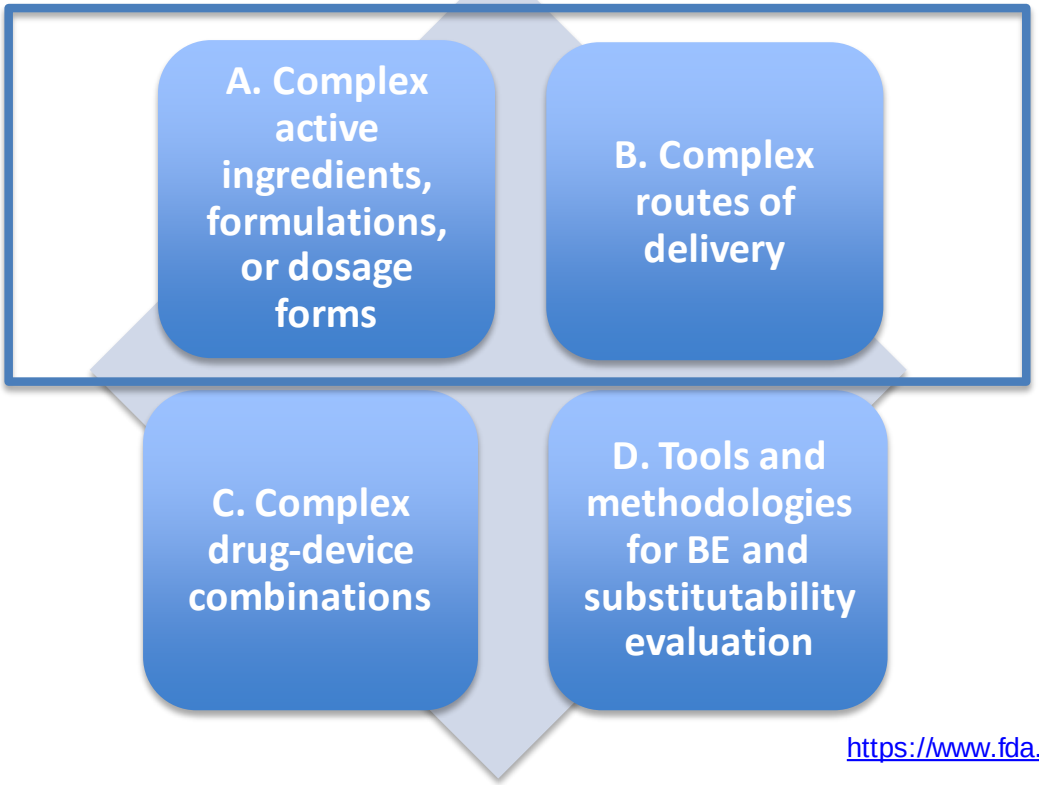


Comparative clinical endpoint BE studies, such as treatment of acne vulgaris, are semi-qualitative assessments of change in condition over a prolonged (e.g., 12-week) period often requiring a placebo control. This gives rise to the need for a large patient population to statistically power the study.

GDUFA Research Science Priority Areas (FY2020)

15 priority areas under 4 broad categories

In Vitro BE Methods →



https://www.fda.gov/media/132370/download

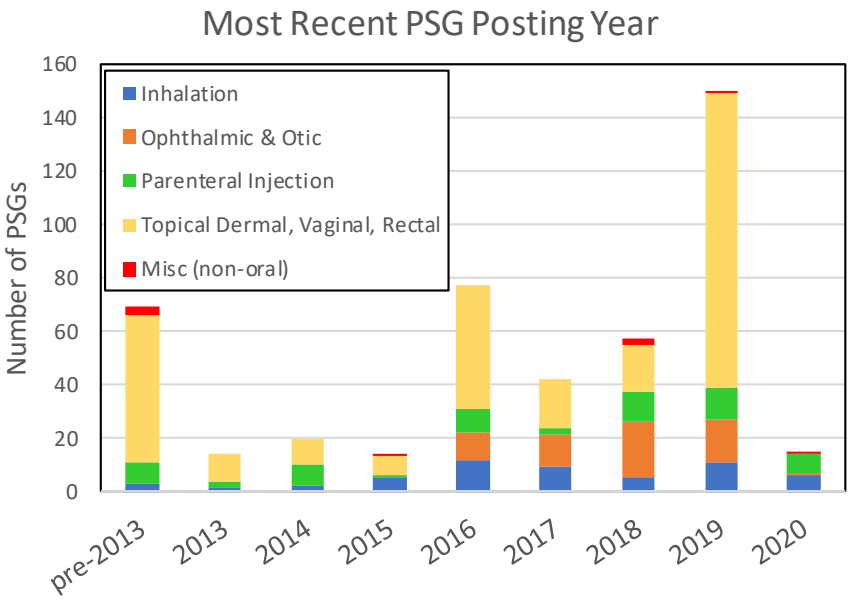
GDUFA II-Funded In Vitro BE Research

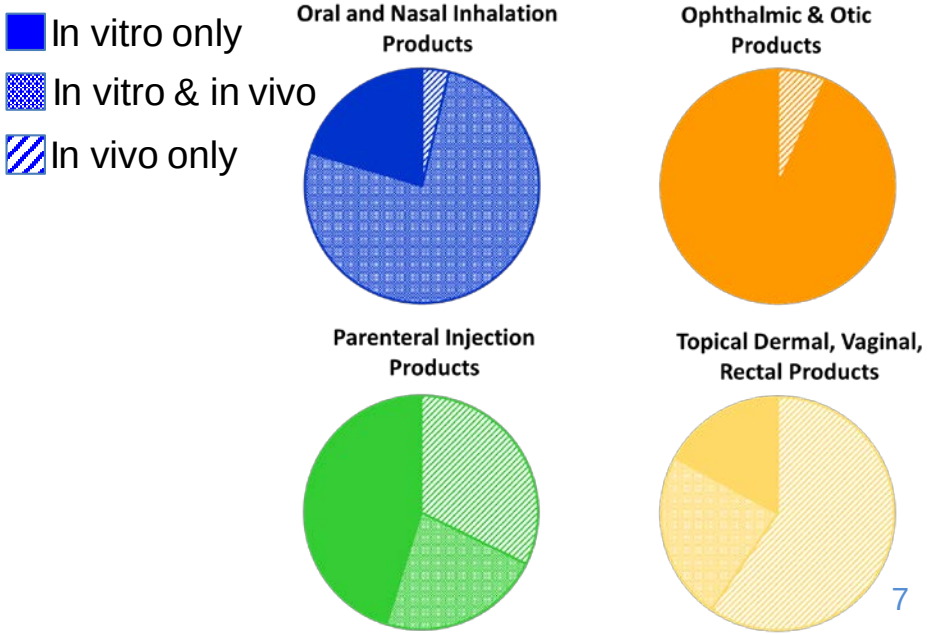
- OGD actively funds and oversees critical research that enables FDA to recommend, review, and approve complex generic products using new and more robust methods to demonstrate BE. This includes in vitro only BE approaches.
- Recent GDUFA-funded research supporting in vitro BE approaches includes:
  - Assessing new analytical methods for characterizing complex formulations and excipients
  - Investigating formulation and manufacturing process parameters on product performance
  - Developing in vitro release testing methods and exploring in vitro-in vivo correlations
  - Developing modeling and simulation methods to support in vitro BE evaluation
- FDA publishes GDUFA outcomes in publicly available annual research reports[1] and through peer-reviewed scientific articles and presentations.
- FDA seeks public feedback on these research aims and solicits research proposals from academic and industry to address these research needs.[2]

1. https://www.fda.gov/drugs/generic-drugs/generic-drugs-research-publications-resources
2. https://www.fda.gov/drugs/generic-drugs/generic-drugs-collaboration-opportunities

GDUFA Research Enables PSG Recommended In Vitro BE Approaches

- PSGs represent FDA's current thinking on appropriate BE studies.
  - FDA recommends in vitro-based approaches as information (research findings) demonstrate the study is an accurate, sensitive, and reproducible measure to ensure bioavailability and BE.





Recent Successes for Generic Orally Inhaled Drug Products (OIDPs)

Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not

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FDA NEWS RELEASE

FDA approves first generic Advair Diskus

For Immediate Release: January 30, 2019

The U.S. Food and Drug Administration today approved the first generic of Advair Diskus (fluticasone propionate and salmeterol inhalation powder) for the twice-daily treatment of asthma in patients aged four years and older and maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Mylan obtained approval to market its generic inhaler in three strengths: fluticasone propionate 100 mcg/ salmeterol 50 mcg, fluticasone propionate 250 mcg/ salmeterol 50 mcg and fluticasone propionate 500 mcg/ salmeterol 50 mcg.

- FDA posted the PSG in 2013
- FDA approved the First Dry Powder Inhaler (DPI) generic in January 2019

Contains Nonbinding Recommendations

Draft Guidance on Albuterol Sulfate

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FDA NEWS RELEASE

FDA approves first generic of ProAir HFA

Agency Supports Development of Complex Generic Drugs to Improve Competition and Access to More Affordable Medicines

For Immediate Release: February 24, 2020

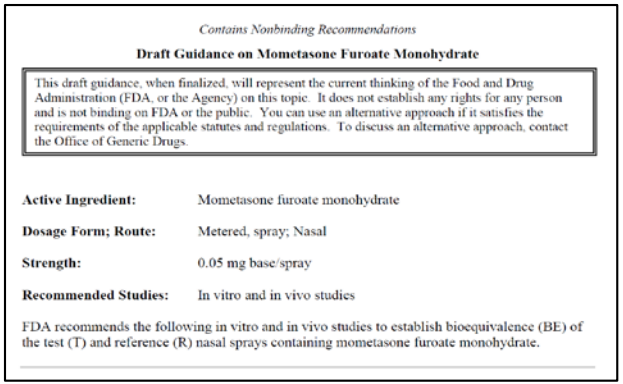
The U.S. Food and Drug Administration today approved the first generic of ProAir HFA (albuterol sulfate) Inhalation Aerosol for the treatment or prevention of bronchospasm in patients four years of age and older with reversible obstructive airway disease and the prevention of exercise-induced bronchospasm in patients four years of age and older.

- FDA posted the PSG in 2013
- FDA approved the First Meter Dose Inhaler (MDI) generic in February 2020

www.fda.gov

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20Proprionate_Salmeterol%20Xinafoate_21077_RC09-13.pdf
https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm630151.htm
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020503.pdf
https://www.fda.gov/news-events/press-announcements/fda-approves-first-generic-proair-hfa

Towards In Vitro BE for OINDPs



Contains Nonbinding Recommendations

Draft Guidance on Mometasone Furoate Monohydrate

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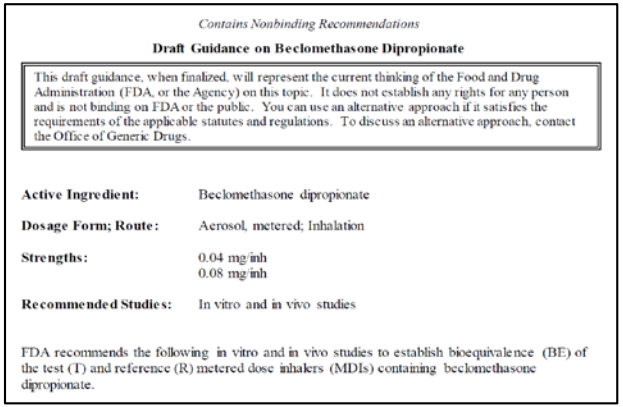
Active Ingredient:	Mometasone furoate monohydrate
Dosage Form; Route:	Metered, spray; Nasal
Strength:	0.05 mg base/spray
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing mometasone furoate monohydrate.



Contains Nonbinding Recommendations

Draft Guidance on Beclomethasone Dipropionate

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Active Ingredient:	Beclomethasone dipropionate
Dosage Form; Route:	Aerosol, metered; Inhalation
Strengths:	0.04 mg/inh 0.08 mg/inh
Recommended Studies:	In vitro and in vivo studies

FDA recommends the following in vitro and in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) metered dose inhalers (MDIs) containing beclomethasone dipropionate.

- Comparative clinical endpoint BE study still poses significant challenges for generic OINDPs
- Alternative approaches incorporated into several nasal suspension PSGs
  - Recommends drug particle size characterization via Morphologically Directed Raman Spectroscopy (MDRS) or other advanced method
  - Supported approval of first generic mometasone furoate monohydrate metered nasal spray, referencing Nasonex.
- Alternative approaches recommended in two PSGs for solution-based meter dose inhaler products (Beclomethasone Dipropionate)
  - Recommends several methods including more realistic aerodynamic particle size distribution testing, dissolution, spray velocity/evaporation characterization, particle morphology imaging, quantitative methods and modeling, and alternative in vivo PK studies.
- Future considerations:
  - What other products are appropriate for alternative BE approach recommendations?
  - What other methods are applicable? New in vitro techniques? More advanced in silico methods?

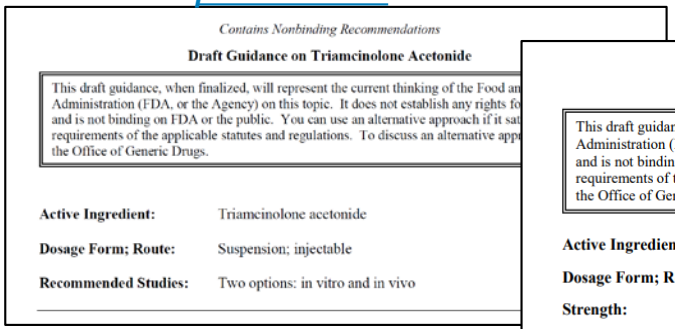
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Mometasone%20furoate%20nasal%20spray%20NDA%20020762%20RV%2002-2019.pdf

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Beclomethasone%20dipropionate%20Inhalation%20Aerosol%20Metered%20NDA%20207921%20PSG%20Page%20RC%20May%202019.pdf

Recent Successes for Generic Parenteral, Ophthalmic, and Otic Products

- In vitro BE studies have been recommended in PSGs where research has indicated that an in vitro approach provides a sensitive, accurate, and robust measure of equivalence.
  - Typically, the in vitro option is a conservative approach based on: 1) comparable formulation composition [21 CFR 314.94(a)(9)]; 2) comparative physicochemical characterization; and 3) in vitro drug release testing, to demonstrate equivalence to the reference product.

parenteral



Contains Nonbinding Recommendations

Draft Guidance on Triamcinolone Acetonide

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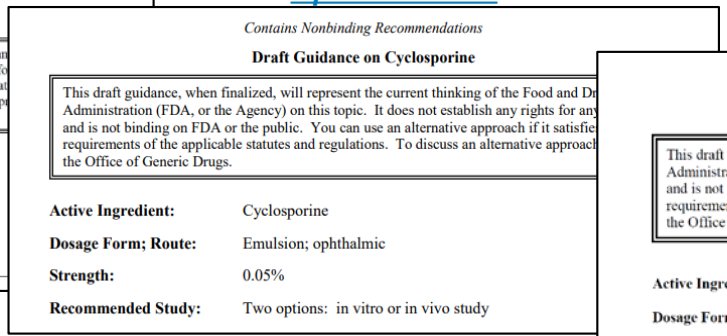
Active Ingredient:	Triamcinolone acetonide
Dosage Form; Route:	Suspension; injectable
Recommended Studies:	Two options: in vitro and in vivo

ophthalmic



Contains Nonbinding Recommendations

Draft Guidance on Cyclosporine

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Active Ingredient:	Cyclosporine
Dosage Form; Route:	Emulsion; ophthalmic
Strength:	0.05%
Recommended Study:	Two options: in vitro or in vivo study

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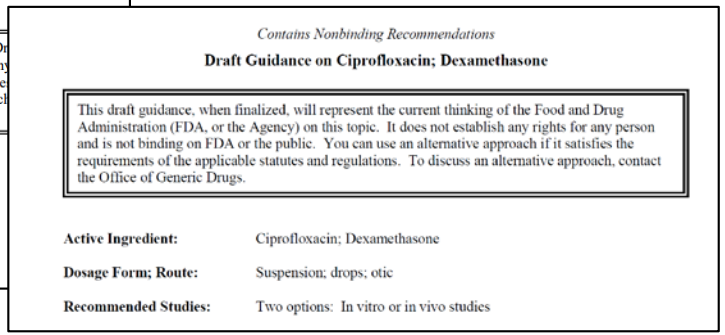

Contains Nonbinding Recommendations

Draft Guidance on Ciprofloxacin; Dexamethasone

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Active Ingredient:	Ciprofloxacin; Dexamethasone
Dosage Form; Route:	Suspension; drops; otic
Recommended Studies:	Two options: In vitro or in vivo studies

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Triamcinolone%20acetonide_injectable%20suspension_NDA%20012041;%20014901_RV07-18.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Cyclosporine_ophthalmic%20emulsion_RLD%20050790_RV09-16.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Ciprofloxacin_Dexamethasone_Otic%20suspension_RLD%20021537_RV04-16.pdf

Towards In Vitro BE for Injectable and Ophthalmic Suspensions

Comparative clinical endpoint for complex ophthalmic products to treat elevated intraocular pressure (IOP) and PK BE studies for long acting parenteral suspensions remain a challenge to appropriately power and assess. Advances in analytical methods, formulation assessment, and better understanding of the impact on in vivo performance ensures that an in vitro BE approach is appropriate.

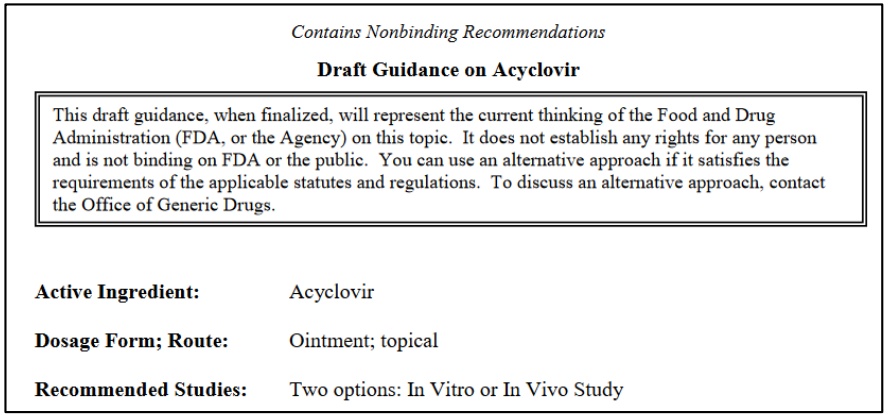
Research Goal:

- Improve current understanding to develop alternative bioequivalence approaches
  - Bioequivalence based on In vitro studies only: a totality of evidence approach
  - Develop in vitro and in vivo correlation
  - Develop alternate statistical approaches for evaluating in vitro characterization data

Scientific Gaps / Research Needs:

- Analytical and statistical challenges with particle size measurements of polydisperse samples and in complex formulations.
- Considerations on in vitro approach for ophthalmic drugs and long-acting injectable drugs: in vitro-in vivo correlations (IVIVCs)? New in vitro techniques? Advanced in silico methods?

Recent Successes for Topical Generics



Contains Nonbinding Recommendations

Draft Guidance on Acyclovir

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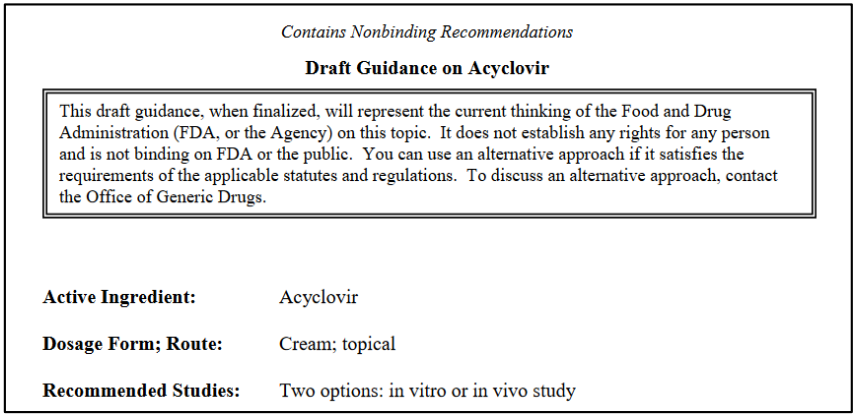
Active Ingredient:	Acyclovir
Dosage Form; Route:	Ointment; topical
Recommended Studies:	Two options: In Vitro or In Vivo Study



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Draft Guidance on Acyclovir

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Active Ingredient:	Acyclovir
Dosage Form; Route:	Cream; topical
Recommended Studies:	Two options: in vitro or in vivo study

- FDA posted the first PSG with an in vitro BE option for a topical product in 2012
- FDA approved the first generic in 2013
- 11 generics approved between 2016-2020, 13 total generic alternatives approved for this product

- FDA posted first PSG with recommendations on in vitro BE characterizations generally applicable to many topical products in 2016
- FDA approved the first generic in 2019
- The in vitro BE recommendations within the PSG are widely used for many topical dermatological products

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_018604.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/psg/Acyclovir_topical%20cream_RLD%2021478_RV12-16.pdf

Towards In Vitro BE for Topical Drug Products

Research is still needed to expand in vitro BE approaches to all topical product areas:

- Creams, Lotions: In Vitro Permeation Testing (IVPT) Study Design & Protocol Standardization
- Solutions and Gels: Thermodynamic Activity Profiles While Drying
- Sprays, Foams: Physicochemical Characterization of Emulsion Foams
- Ointments, Oils: Impact of Molecular Heterogeneity on BA/BE
- Shampoos: IVPT Challenges with Scalp Skin
- Patches, Tapes, and Films: Assessing Adhesion, Irritation, Sensitization
- Suppositories and Enemas: Physicochemical Characterization of Unique Dosage Forms
- Rectal and Vaginal Inserts: In Vitro Characterization of Local BA/BE

Breakout Session 3: Discussion on Knowledge Gaps and Research Needs for In Vitro Bioequivalence

- Analytical methods
  - Developing and verifying new analytical methods to assess complex formulation properties
    - Particle size, rheology, phase structure, and drug partitioning and release
  - Establishing best measurement and comparison practices
    - Data to demonstrate method appropriateness and sensitivity, statistical methods to deal with outlier data and comparing complex data profiles to demonstrate sameness
- Establishing in vitro-in vivo correlations/relationships (IVIVC / IVIVR), where needed.
  - An IVIVC/IVIVR may be appropriate for products that have complex, or proposed differences in, formulation properties and a PK, PD and/or comparative clinical endpoint study is considered to provide an accurate means to demonstrate BE
- Information / predictive models on how differences in product formulation and physicochemical properties impact product quality and BE

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