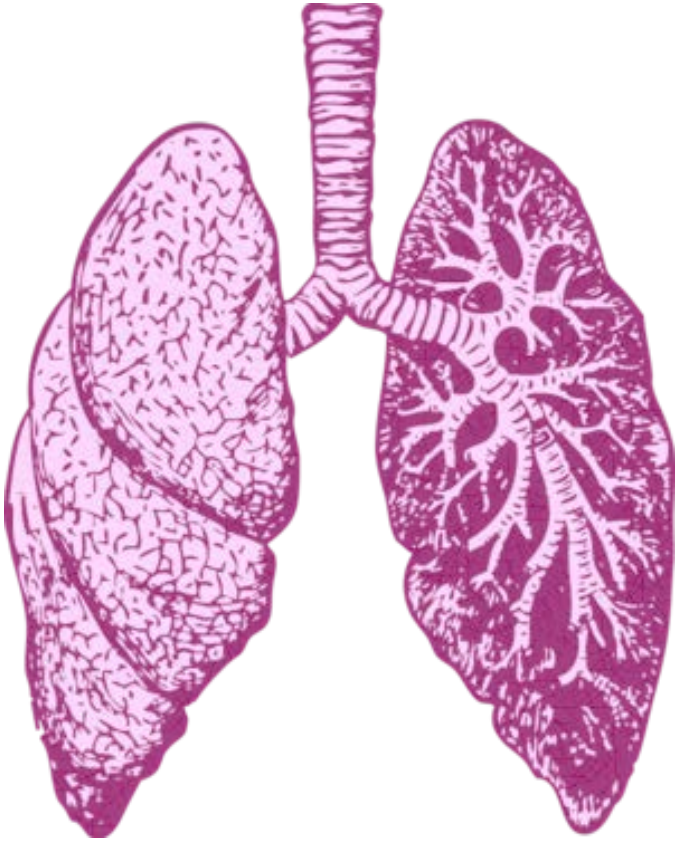


ATS 2018

Session L25

May 23, 2018

GENERIC DRUG DEVELOPMENT FOR RESPIRATORY PRODUCTS, US FOOD AND DRUG ADMINISTRATION UPDATE

Disclaimer

- *In this presentation we are relaying personal views and opinion. This presentation is not intended to convey official U.S. FDA policy, and no official support or endorsement by the U.S. FDA is provided or should be inferred.*

- *The materials presented are available in the public domain.*

Purpose

This session will describe development of orally inhaled and nasal drug products (OINDPs) focusing on paths forward to make safe, efficacious, and cost-effective generic respiratory and nasal products available to the American public.

Session Objectives

- To recognize key aspects of generic drug regulatory approval process and how the Office of Generic Drugs (OGD) evaluates bioequivalence for complex inhaled generic drug products, using a weight-of-evidence approach
- To articulate how emerging technologies and innovative approaches are being utilized for FDA-funded research, FDA guidance development, and regulatory decision-making
- To describe product-specific guidances (PSGs) for generic drug products recently posted by the FDA, with a focus on how these guidances can inform complex orally-inhaled and nasal generic drug development

Session Outline

- Regulatory perspective for generic drug product development
- Generic Drug User Fee Amendments (GDUFA)
- Approach to determine bioequivalence for OINDPs
- GDUFA research initiatives
- Product-specific guidances
- Conclusions
- Questions

OVERVIEW OF FDA GENERIC DRUG APPROVAL PROCESS, REGULATORY SCIENCE RESEARCH, AND EMERGING CONCEPTS

Kimberly Witzmann, MD
Office of Research and Standards
Office of Generic Drugs, CDER, FDA

Generic Drugs – what are they?

- Are “copies” of brand name drugs
- Are the same as those brand name drugs in dosage form, safety, strength, route of administration, quality, performance characteristics, and intended use

From FDA website – Understanding Generic Drugs
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/UnderstandingGenericDrugs/default.htm

Drug Competition Action Plan (DCAP)- To Improve Drug Access

- Announced by FDA's Commissioner, Dr. Scott Gottlieb, in June 2017
- Goal is to bring more competition to drug market as a way to improve drug access
- This plan has three main components:
  - **Reducing gaming by branded companies** that can delay generic drug entry;
  - **Resolving scientific and regulatory obstacles** that can make it difficult to win approval of generic versions of certain complex drugs;
  - **Improving efficiency and predictability of FDA's generic review process** to reduce the time it takes to get a new generic drug approved and lessen the number of review cycles undergone by generic applications before they can be approved

https://blogs.fda.gov/fdavoice/index.php/2017/06/fda-working-to-lift-barriers-to-generic-drug-competition/

Drug Competition Action Plan (DCAP)-

- Reducing gaming by branded companies…
- Resolving scientific and regulatory obstacles…
- Improving the efficiency and predictability of the FDA's generic review process…

https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm564725.htm

Reducing the Hurdles for Complex Generic Drug Development

Posted on **October 2, 2017** by **FDA Voice**

By: Scott Gottlieb, M.D.

Earlier this year, I announced our Drug Competition Action Plan to advance new policies aimed at bringing more competition to the drug market. My goal was to improve access consumers have to the medicines that they need. I consider access to medicine a matter of public health. If consumers are priced out of the drugs they need, that's a public health concern that FDA should address, within the scope of its mandate and authorities.

While FDA doesn't control drug pricing, our policies do affect competition in the market. This is the nexus of our current efforts on drug pricing.

Our plan has a number of different domains. Among them is a compilation of efforts to improve the efficiency of the generic drug approval process; and another is a group of

GDUFA II Public Workshops

Oct 2017

- Leveraging Quantitative Methods and Modeling to Modernize Generic Drug Development and Review
- Demonstrating Equivalence of Generic Complex Drug Substances and Formulations
- Topical Dermatological Generic Drug Products: Overcoming Barriers to Development and Improving Patient Access

Jan 2018

- New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products

Future Workshops in 2018 and 2019:

Sept 2018

- SBIA complex product "boot camp"

Oct 2018

- FDA/DIA Combination products

Mar 2019

- PBPK modeling for locally-acting products

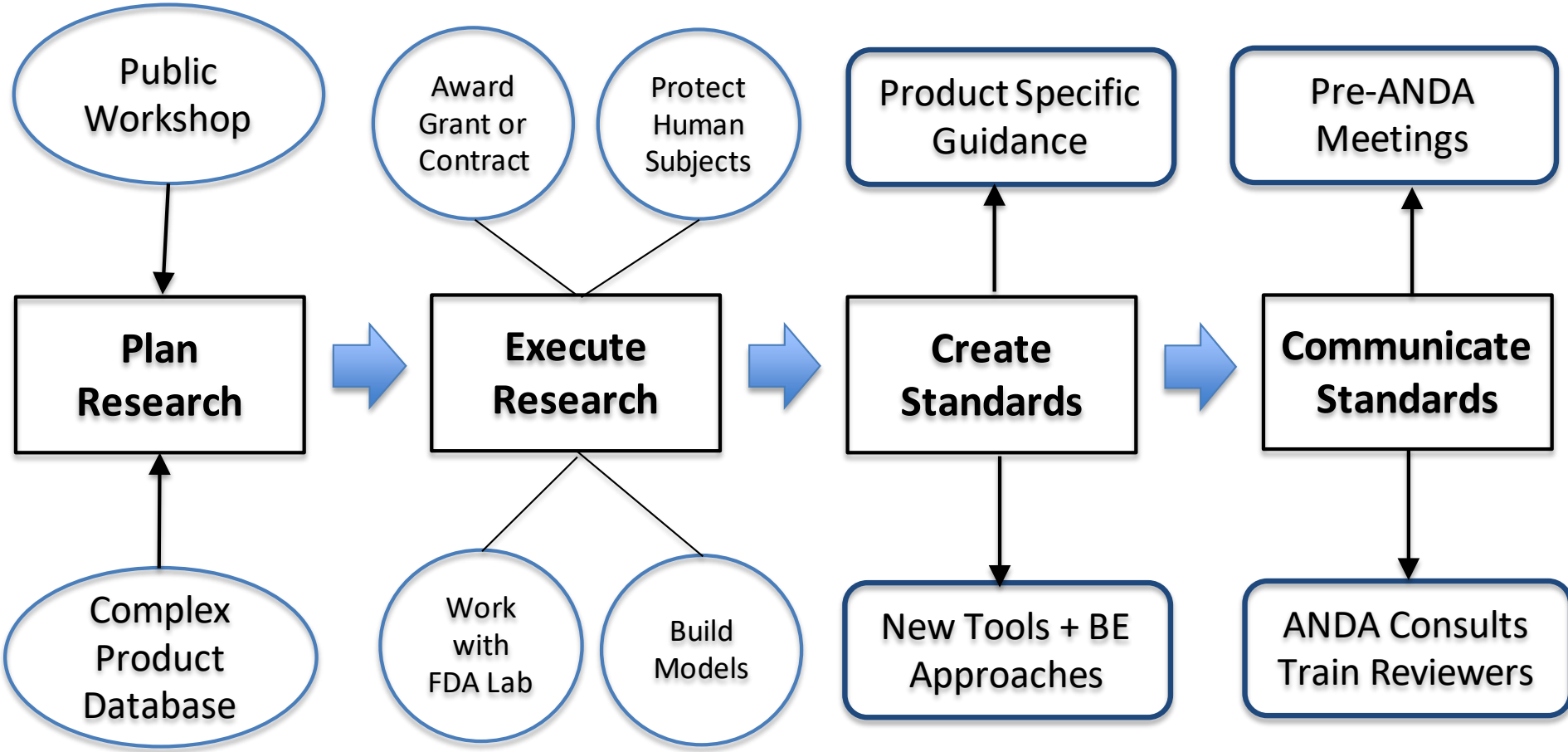
https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/genericdrugs/ucm567695.htm

Office of Generic Drugs

- Located in the Center for Drug Evaluation and Research
- Offices of Bioequivalence, Regulatory Operations, Generic Drug Policy, Research and Standards
- Office of Research and Standards – leads the implementation of regulatory science commitments and translates research results into standards for safe, effective, and equivalent generic drugs

Office of Research and Standards Operational Model

- ORS is a multidisciplinary **Office** that plans and conducts **Research** and translates the results into generic drug **Standards**



Generic Drug User Fee Amendments (GDUFA)

- Title III of the Food and Drug Administration Safety and Innovation Act (Public Law 112-144)
- Passed in July 2012 to speed access to safe and effective generic drugs to the public and reauthorized by FDARA in August 2017
- Requires user fees to supplement costs of reviewing generic drug applications and provides additional resources, including for regulatory science research
- GDUFA Regulatory Science program is designed to stimulate innovation and growth in the generic drug field
  - Identify, study, and implement new methodologies and tools
  - Generate evidence to support efficient review and approval of ANDAs
- FDA annual public workshop solicits stakeholder input on research priorities for generic regulatory science initiatives

https://www.fda.gov/ForIndustry/UserFees/GenericDrugUserFees/default.htm

Generic Drug Product Substitutability

In relation to the Reference Listed Drug, generic products are expected to be:

- **Pharmaceutically Equivalent (PE)**

  The same active ingredient, dosage form, strength, route of administration, and meet the same compendial standards (strength, quality, purity, and identity)

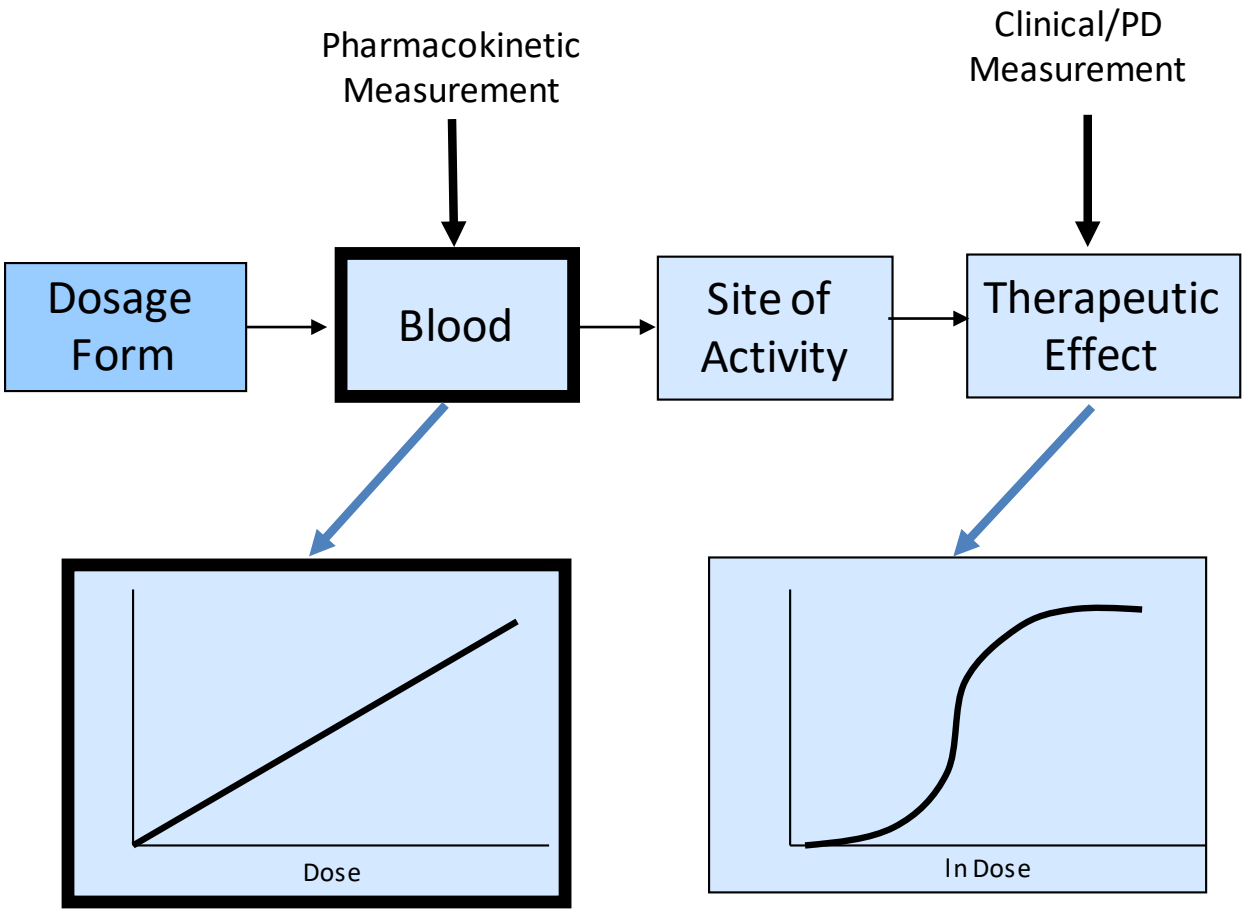
- **Bioequivalent (BE)**

  No significant difference in the rate and extent of absorption of the active ingredient at the site of action

- **Therapeutically Equivalent (TE)**

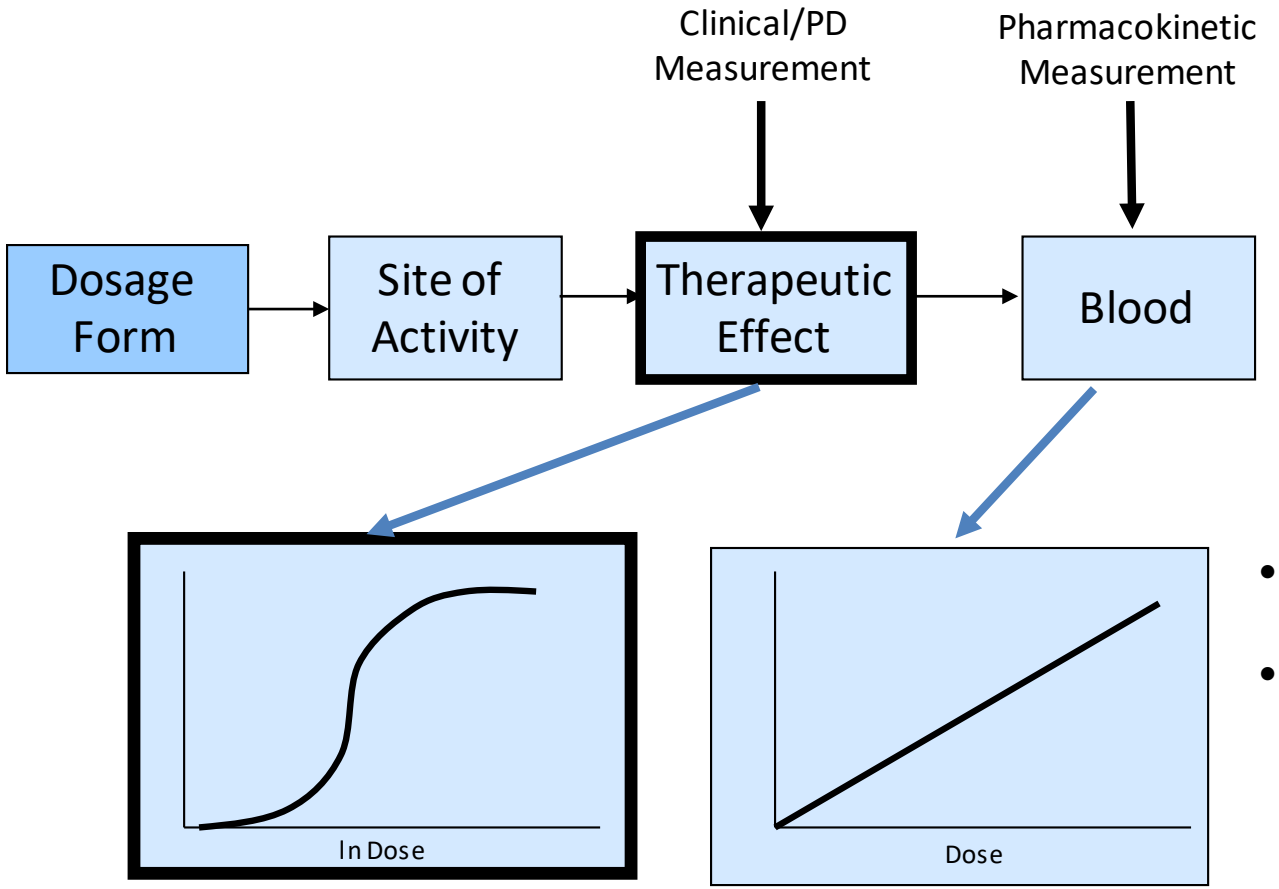
  Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling

BE for Systemically Acting Drugs



- Delivered to the bloodstream for distribution to site(s) of action in the body
- BE determined with PK studies
  - Relatively short studies
  - Relatively small number of subjects

BE for Locally Acting Drugs



- Not intended to be absorbed into the bloodstream
- Delivered directly to sites of action (lung)

OINDPs: Weight-of-Evidence Approach

- Includes the following:
  - Qualitative and Quantitative sameness of formulation
  - In vitro comparative studies
  - In vivo PK studies
  - PD or comparative clinical endpoint study
  - Device substitutability
- Incomplete understanding of the relevance of results from BE studies to drug concentrations at local site of action in lung
- Residual uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE

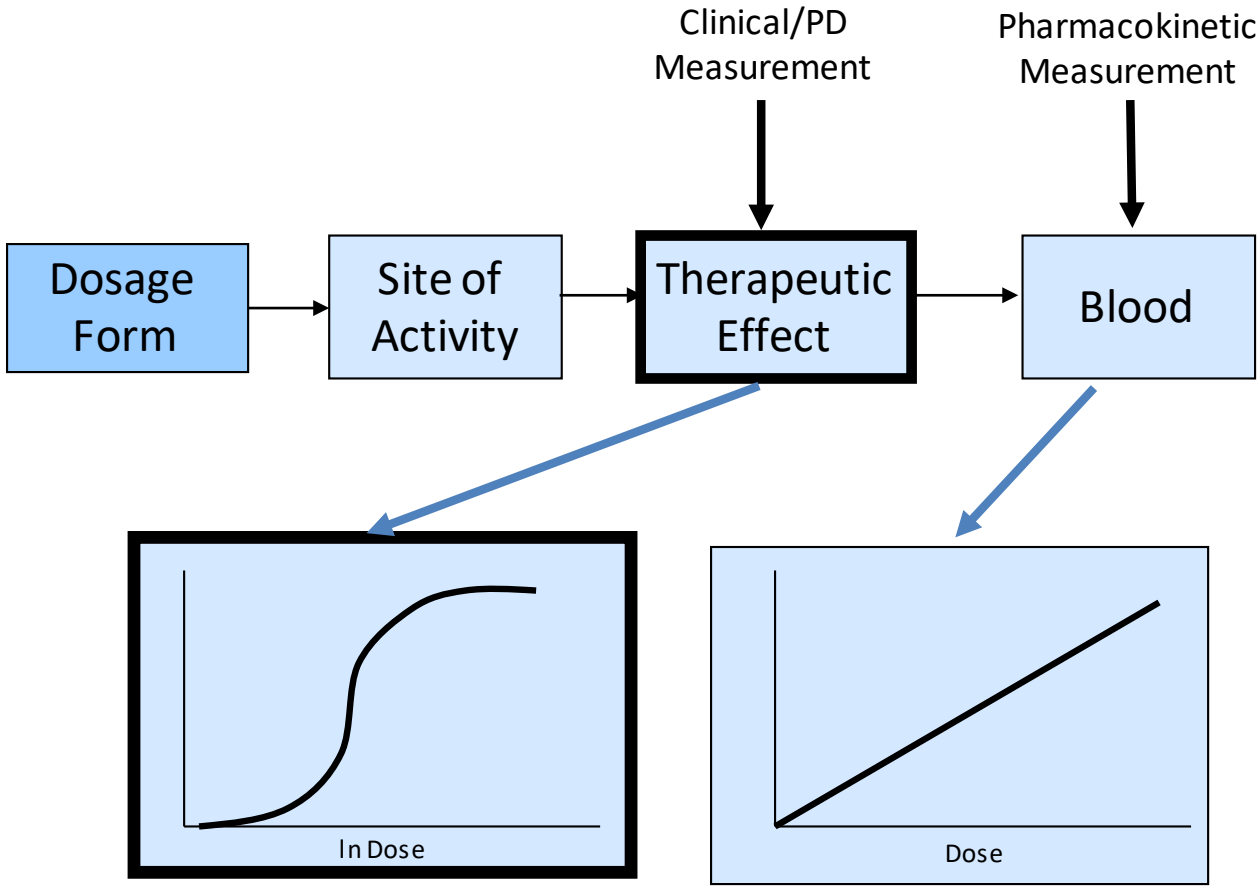
Formulation Considerations

- Qualitative (Q1) sameness
  - Same inactive ingredient(s)
    - Critical to establishing equivalence between the test and reference DPI products
    - Limited choices of inactive ingredients for DPIs
- Quantitative (Q2) sameness
  - Same inactive ingredient(s) but may differ in concentration
    - Cannot exceed the levels used in other FDA approved products administered by the same route of administration
    - Effect of Q2 difference on bioequivalence assessed by in vitro and in vivo BE studies
    - Submit pharmaceutical development data to support the selected test formulation

In Vitro Considerations

- Single Actuation Content (SAC) and aerodynamic particle size distribution (APSD)
  - Critical attributes that are believed to affect the total and regional deposition of drugs in the lung
- SAC and APSD dependent on, and sensitive to, product- and process-related factors
  - Physicochemical properties of API(s) and carrier
  - Device properties
  - Process conditions

Pharmacokinetic Studies



The sampling site for PK studies (plasma) is downstream of the site of action (the lung)

In Vivo Pharmacokinetics

PK BE study objective

- Reliable and sensitive method to determine differences in drug product characteristics
- Single-dose studies in healthy subjects for all strengths
- Dose based on minimizing the number of inhalations, but justified by assay sensitivity
- Relation between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood, **therefore all strengths are needed**

In Vivo Pharmacodynamics

- Dose-response PD BE study preferred over a comparative BE study with clinical endpoint
- PD study used if there is adequate dose-response (short-acting β-agonists)
- Dose-response ensures the sensitivity of a PD study to distinguish potential differences between test and reference products
- Establishing dose-response for inhaled corticosteroids has been challenging
- Comparative BE clinical studies for products which do not demonstrate adequate dose-response

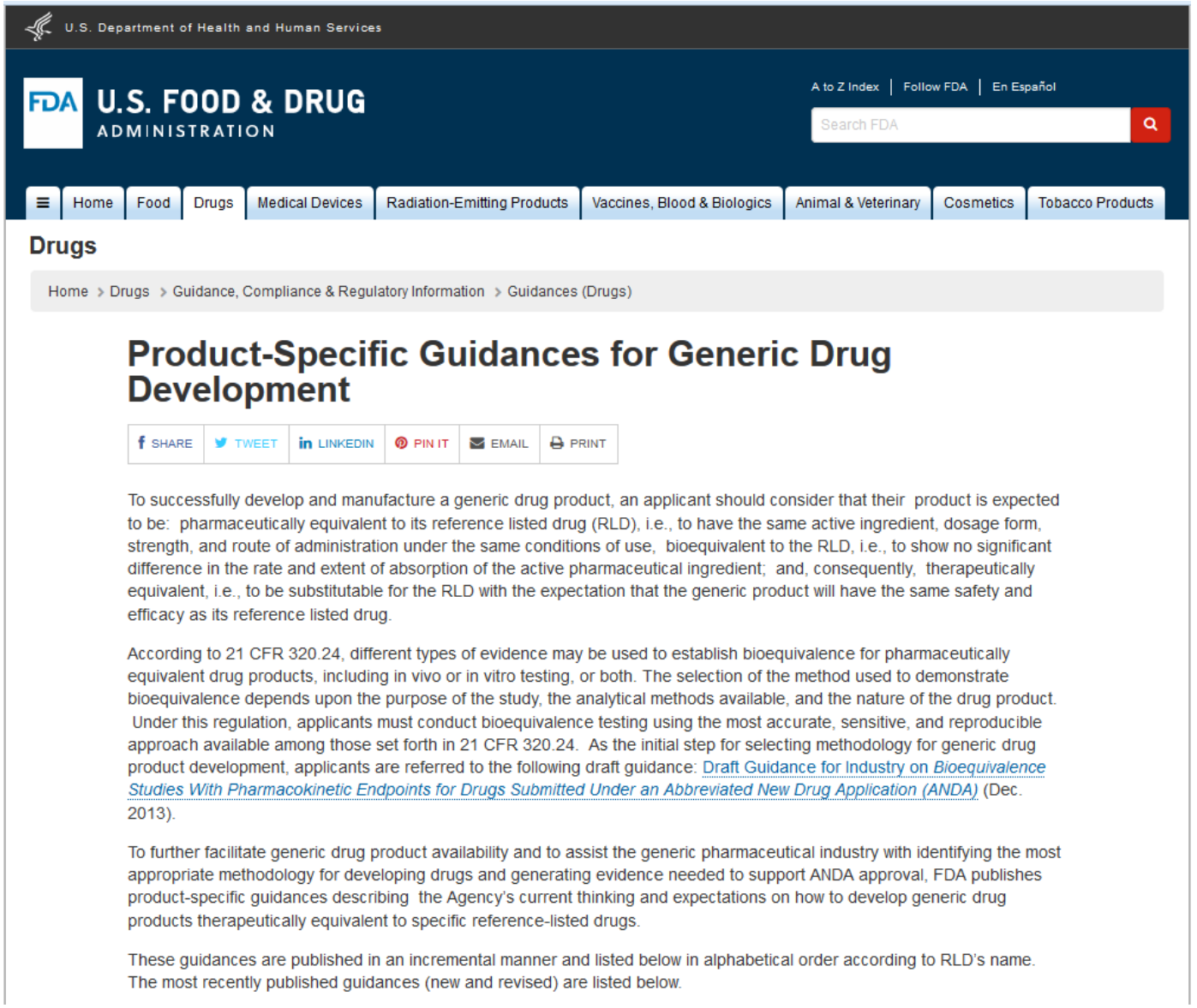
Comparative BE Clinical Endpoint Study

- Different from NDA Phase 3 study
- Three arms: Test, Reference, placebo control
- Comparison demonstrates sensitivity
- Lowest labeled dose
- Relies on RLD for safety and efficacy
- Study in one indicated population
- BE met if 90%CI for T/R ratio for endpoints falls within 80.00-125.00%

Comparative BE Clinical Endpoint Study

- Less sensitive than other methods for BE
- Patients are more variable
- Must meet the established BE limits
- May require several hundred patients
- Study duration may be several weeks depending upon the approved labeling
- Expensive to conduct
- Product-Specific Guidances based on data from RLD programs

Product-Specific Guidances



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Guidance, Compliance & Regulatory Information > Guidances (Drugs)

Product-Specific Guidances for Generic Drug Development

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

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 referred to the following draft guidance: Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference-listed drugs.

These guidances are published in an incremental manner and listed below in alphabetical order according to RLD's name. The most recently published guidances (new and revised) are listed below.

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Complex Orally Inhaled Drug Products: Weight-of-Evidence Approach

2013
No generic OIDP products;
1st product-specific guidance for OIDP published

Device and Formulation Design

Comparative In Vitro Studies

Comparative Pharmacokinetic Studies

Comparative Pharmacodynamics or Clinical Endpoint Studies

2017
>50% of all OIDPs have PSGs;
OIDP ANDA applications reviewed

Generic Drug Product Substitutability

In relation to the Reference Listed Drug, generic products are expected to be:

- **Pharmaceutically Equivalent (PE)**

  The same active ingredient, dosage form, strength, route of administration, and meet the same compendial standards (strength, quality, purity, and identity)

- **Bioequivalent (BE)**

  No significant difference in the rate and extent of absorption of the active ingredient at the site of action

- **Therapeutically Equivalent (TE)**

  Can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling

Drug-Device Combination Products

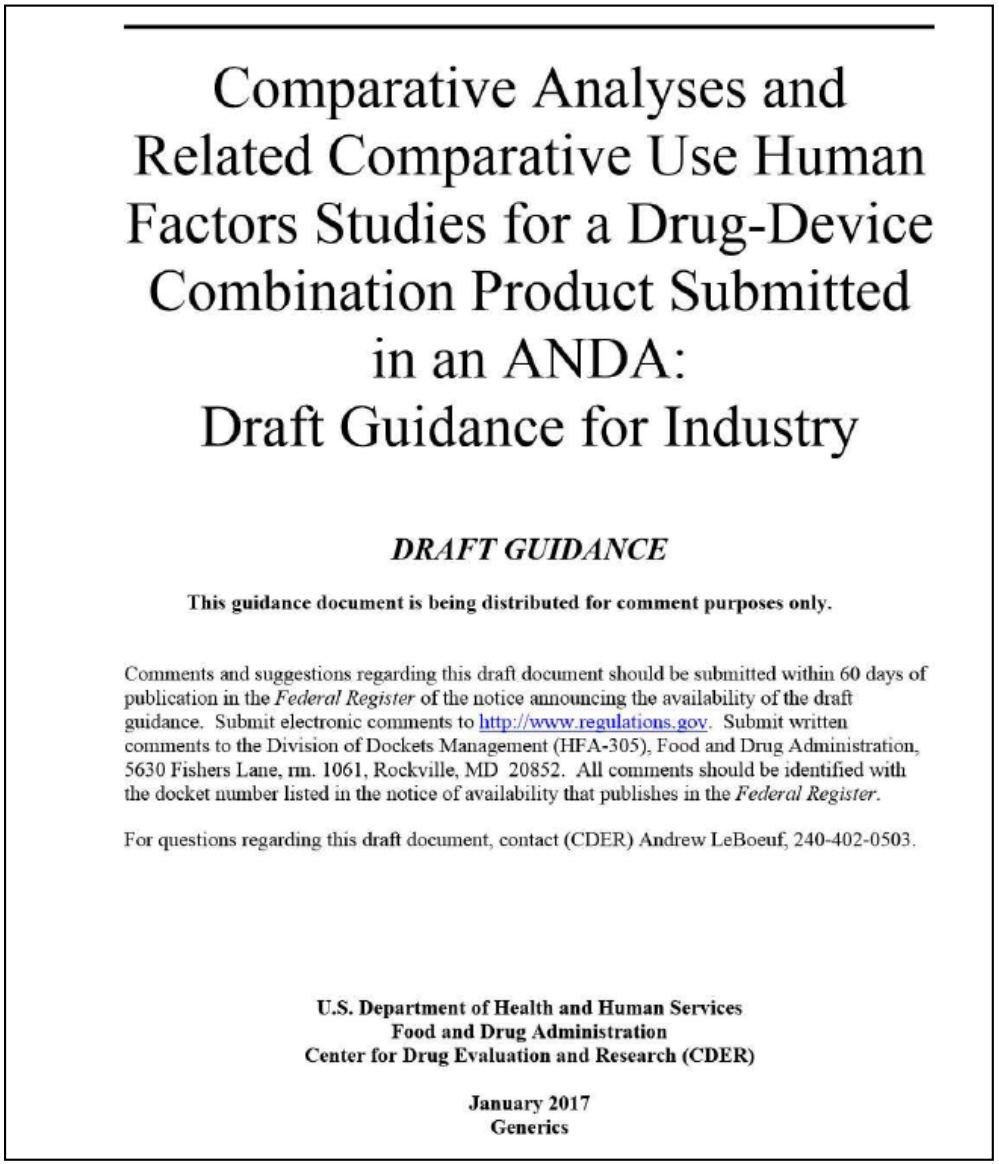
Complex Generic Drug-Device Combination Products

- Therapeutically equivalent: can be substituted with the full expectation that the generic product will produce the same clinical effect and safety profile as the RLD under the conditions specified in labeling
- **Same** expectation for generic drug-device combination products
- Generic and RLD do not need to be identical, as long as differences do not preclude approval under an ANDA
- FDA expects that end-users can use the generic combination product when it is substituted for the RLD without the intervention of the health care provider and/or without additional training prior to use of the generic combination product

How has GDUFA research impacted OGD's advice for development and review of complex generics?

- Research informs our Guidance and PSGs to further facilitate generic drug product availability, and to assist industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval
  - PSGs describe the Agency's current thinking and expectations for how to develop generic drug products that are therapeutically equivalent to their RLDs
- Research also informs our Guidance development as well as Pre-ANDA communications with applicants

Guidance for Complex Drug-Device Products- User Interface



Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA:
Draft Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Andrew LeBoeuf, 240-402-0503.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2017
Generics

User Interface

Refers to all components of a product with which a user interacts, such as labels and packaging, the delivery device constituent part, and any associated controls and displays

External Critical Design Attributes

Refers to those features that directly affect how users perform a critical task that is necessary in order to use or administer the drug product

Comparative Analyses

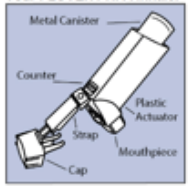
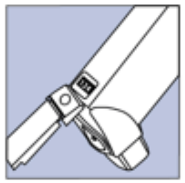
1. Labeling Comparison
2. Comparative Task Analysis
3. Physical Comparison of Delivery Device Constituent Part

Labeling Comparison

- Side-by-side, line-by-line comparison of the full prescribing information, instructions for use, and descriptions of the delivery device constituent parts of the generic combination product and its RLD

- Labeling differences that stem from permissible differences in design between the user interface for the proposed generic combination product and its RLD may fall within the scope of permissible differences in labeling for a product approved under an ANDA [21CFR 314.94(a)(8)(iv)]

Sample Labeling Comparison

IFU of Flovent® HFA	Proposed T product IFU
Your FLOVENT HFA inhaler  **Figure A**  **Figure B** • The metal canister holds the medicine. **See Figure A.** • The metal canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the plastic actuator. **See Figure B.** • The counter starts at **124**. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at **000**. • **Do not try to change the numbers or take the counter off the metal canister.** The counter cannot be reset, and it is permanently attached to the metal canister. • The dark orange plastic actuator sprays the medicine from the metal canister. The plastic actuator has a protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the metal canister is not in use. The strap keeps the cap attached to the plastic actuator. • **Do not** use the plastic actuator with a canister of medicine from any other inhaler. • **Do not** use a FLOVENT HFA metal canister with an actuator from any other inhaler.	[YOUR PROPOSED LABEL HERE]
Before using your FLOVENT HFA inhaler • The inhaler should be at room temperature before you use it. • If a child needs help using the inhaler, an adult should help the child use the inhaler with or without a valved holding chamber, which may also be attached to a mask. The adult should follow the instructions that came with the valved holding chamber. An adult should watch a child use the inhaler to be sure it is used correctly.	[YOUR PROPOSED LABEL HERE]
Priming your FLOVENT HFA inhaler  **Figure C**  **Figure D** • **Before you use FLOVENT HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.** • To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray the inhaler 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.** • Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **120**. **See Figure D.** • You must prime your inhaler again if you have not used it in more than 7 days or if you drop it. Take the cap off the mouthpiece and shake the inhaler well for 5 seconds. Then spray it 1 time into the air away from your face.	[YOUR PROPOSED LABEL HERE]

https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021433s033lbl.pdf

Comparative Task Analysis

- Comparative task analysis is assessed between the RLD and the proposed generic drug-device combination product

- Critical tasks are user tasks that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care

Physical Comparison of Delivery Device

- Visual and tactile examination of the physical features of the RLD
- Compare them to those of the delivery device constituent part for the proposed generic combination product
- Size, shape, visual or tactile feedback

Assessment of Identified Differences

- Consider any identified differences between the user interface of a proposed generic combination product and its RLD in the context of the *overall risk profile* of the product
- **No Differences**
- **Minor Differences**
  - Guidance describes a design difference as minor if the differences in the user interface of the proposed generic combination product, in comparison to the user interface of the RLD, do not affect an external critical design attribute
- **Other Differences**
  - FDA may not view a design difference as minor if any aspect of the threshold analyses suggests that differences in the design of the user interface of a proposed generic combination product as compared to the RLD *may* impact an external critical design attribute that involves administration of the product

Assessment of Identified Differences

In instances when *other than minor* differences are identified:

- Consider re-design of the user interface to minimize differences from the RLD
- Potential need for additional information and/or data to support the ANDA submission

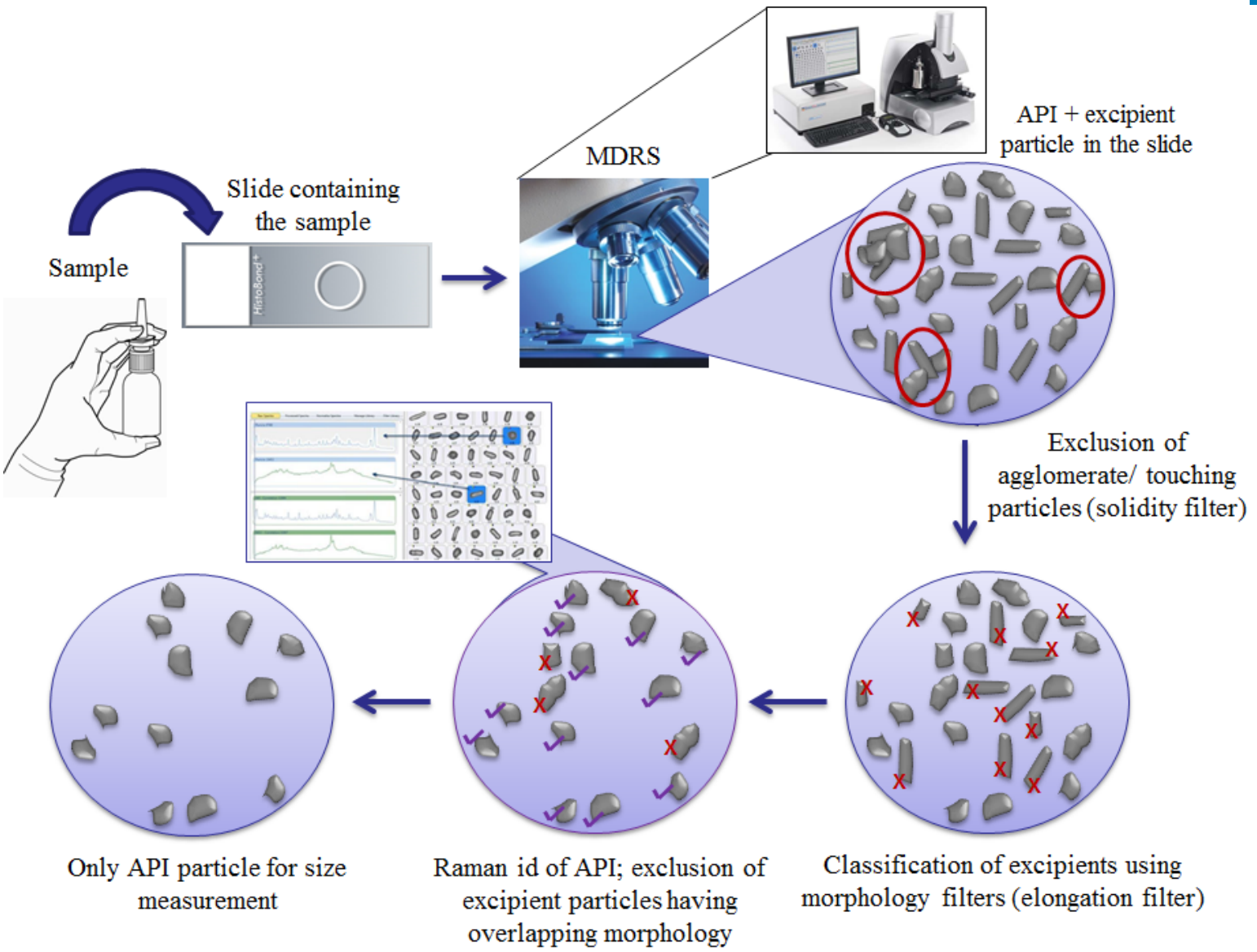
Draft guidance recommends that potential applicants contact FDA through a pre-ANDA submission/controlled correspondence *before* conducting comparative use human factors studies

How has GDUFA research informed ANDA review of complex generics?

- Research has informed our ANDA review process
- By studying novel approaches to difficult scientific questions, we have been able to use a novel particle size method (MDRS) to support BE review for complex nasal suspension products, which precluded an applicant from repeating a comparative clinical endpoint study, and led to ANDA approval for the first generic mometasone furoate nasal suspension [RLD: Nasonex® NDA 20-762]

MDRS: Morphologically-Directed Raman Spectroscopy

MDRS: How does it work?



MDRS: Morphologically-Directed Raman Spectroscopy

Courtesy of Dr. Abir Absar, Ph.D. (FDA/OCP)

Triamcinolone Acetonide Nasal Suspension

Contains Nonbinding Recommendations

Draft Guidance on Triamcinolone Acetonide

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:	Triamcinolone acetonide
Dosage Form; Route:	Metered spray; nasal
Prescribing Information:	Over-the-counter (OTC)
Recommended Studies:	In vitro and in vivo studies

Alternate approach to the comparative clinical endpoint study:

A clinical endpoint BE study is recommended for T triamcinolone acetonide nasal spray product because of an inability to adequately characterize drug particle size distribution (PSD) in aerosols and sprays using commonly used analytical methods. Drug PSD in suspension formulations has the potential to influence the rate and extent of drug availability to nasal sites of action and to systemic circulation. If drug PSD in the T and R products can be accurately measured using a validated analytical method such as morphology directed Raman spectroscopy or any other advanced methodology, sponsors may submit comparative particle size distribution data as part of their drug characterization within their ANDA application.. In such case, comprehensive method validation data should be submitted to demonstrate the adequacy of the selected method in identifying and measuring the size of the drug particles without any interference from the excipient particles that are also suspended in the formulation. An orthogonal method may be required if the selected methodology is not sensitive to measure particles beyond a certain size range. Equivalence between T and R drug PSD should be based on PBE analysis on D_{50} and span.

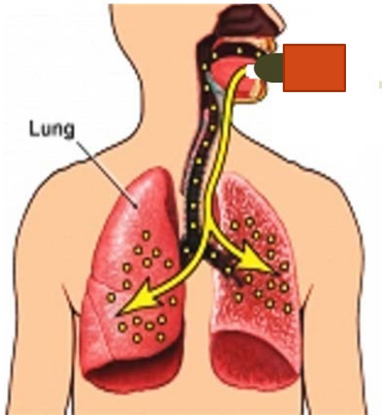
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520271.pdf

Where are we going for the future of complex generics?

- The future will concentrate on better methods, and better pre-ANDA communications
- Continuing research for complex generic products will further the methods
- Better pre-ANDA communications will help to inform and educate applicants to submit more scientifically robust initial ANDAs, and decrease the number of review cycles to approval for these complex products

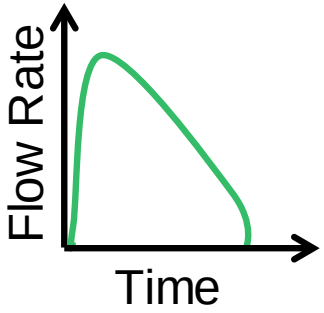
Better Methods: Clinically Relevant APSD In Vitro Test

A more realistic in vitro APSD method is important for pharmaceutical development and quality control of OIDPs

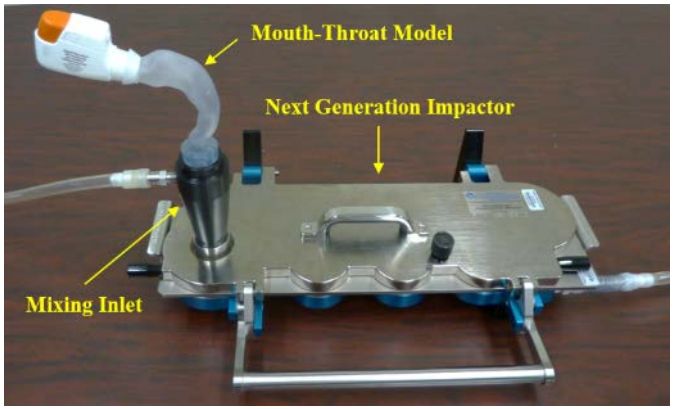


http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

Realistic mouth-throat (MT) models



Representative inhalation profiles (IP)



In vitro APSD method more predictive of in vivo deposition

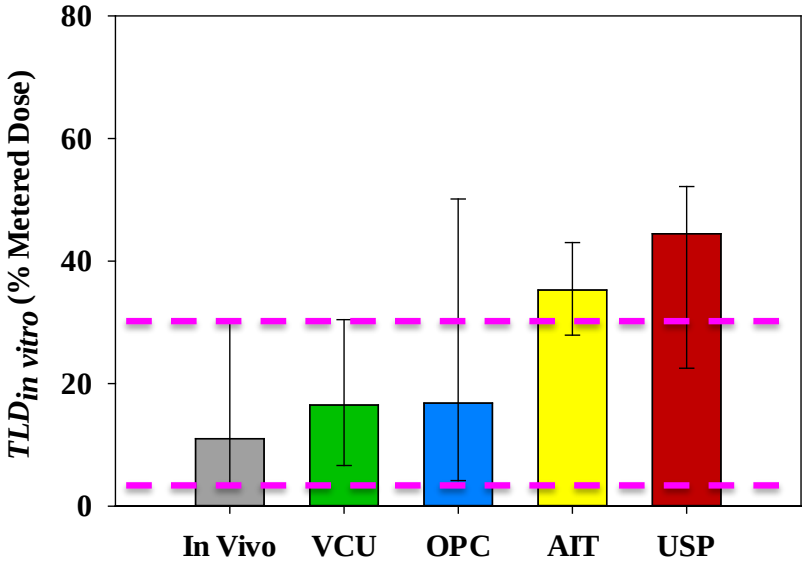
APSD: Aerodynamic Particle Size Distribution

Research Grant #1U01FD005231-01 described at https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm592245.htm

Better Methods: MDI Results

In vitro - in vivo total lung deposition (TLD) comparison

- VCU and OPC: good prediction
- AIT and USP: over-prediction



MDI: metered dose inhaler

Research Grant #1U01FD005231-01 described at
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm592245.htm

Better Methods: Research Conclusions

- A more realistic APSD in vitro test for OIDPs provides a better prediction of where inhaled particles may be deposited in the lungs compared to the current APSD in vitro test which uses the USP inlet
- Importance for generic OIDPs
  - Product development
  - Quality control
  - Faster, less expensive and more sensitive method compared to Comparative BE clinical endpoint bioequivalence studies

APSD: Aerodynamic Particle Size Distribution; OIDP: orally-inhaled drug product

Better Communications: Pre-ANDA Program for Complex Products Under GDUFA II

- Clarify regulatory expectations for prospective applicants early in product development
- Help applicants develop more complete submissions
- Promote a more efficient and effective review process
- Reduce the number of review cycles necessary to obtain ANDA approval of complex products

Pre-ANDA Interactions with FDA for Complex Products Under GDUFA II

- General Guidances
  - *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf
- Product Specific Guidances
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
- Controlled Correspondences
  - *Controlled Correspondence Related to Generic Drug Development* (Nov 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm583436.pdf
- Pre-ANDA meetings
  - *Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Controlled Correspondence

- Requests for information on a specific element of generic drug product development
- Specific types of requests within scope
  - Related to Inactive Ingredient Database
  - Q1/Q2 formulation assessment
  - Related to product quality
  - Comparative analyses of proposed user interface
- Guidance
  - *Controlled Correspondence Related to Generic Drug Development* (Nov 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm583436.pdf

Pre-ANDA Meetings

- **Product Development**
  - Annually throughout product development
  - Proposed study design
  - Alternative approach
  - Additional study expectations
- **Pre-submission**
  - 6 months before proposed submission
  - Discuss content and format of package to be submitted
  - Data to support equivalence claims
  - Types of data to include
  - Identification of items to be clarified in submission of ANDA

- Guidance
  - *Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct 2017)
  - https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm578366.pdf

Conclusions

- Explained the determining factors of bioequivalence for locally-acting drugs, and the current weight-of-evidence approach for OINDPs
- GDUFA research goals are to identify, study, and implement new tools and methodologies, and to generate evidence to support efficient review and approval of ANDAs
- Additional resources under GDUFA II for complex generics
- Regulatory science research informs PSGs, and helps provide expectations for how to develop generic drug products that are therapeutically equivalent to their RLDs
- Research informs Pre-ANDA interactions, and GDUFA II allows applicants more ways to communicate with FDA before ANDA submission
- Regulatory science research supports ANDA approvals
- Future Directions:
  - Better Methods
  - Better Pre-ANDA Communications


FDA
U.S. FOOD & DRUG
ADMINISTRATION

UPDATES ON PRODUCT-SPECIFIC GUIDANCES FOR OINDPS

Bryan Newman, PhD

Inhalation and Drug-Device Combination Products Team

Office of Research and Standards, Office of Generic Drugs

CDER, Food and Drug Administration

Outline

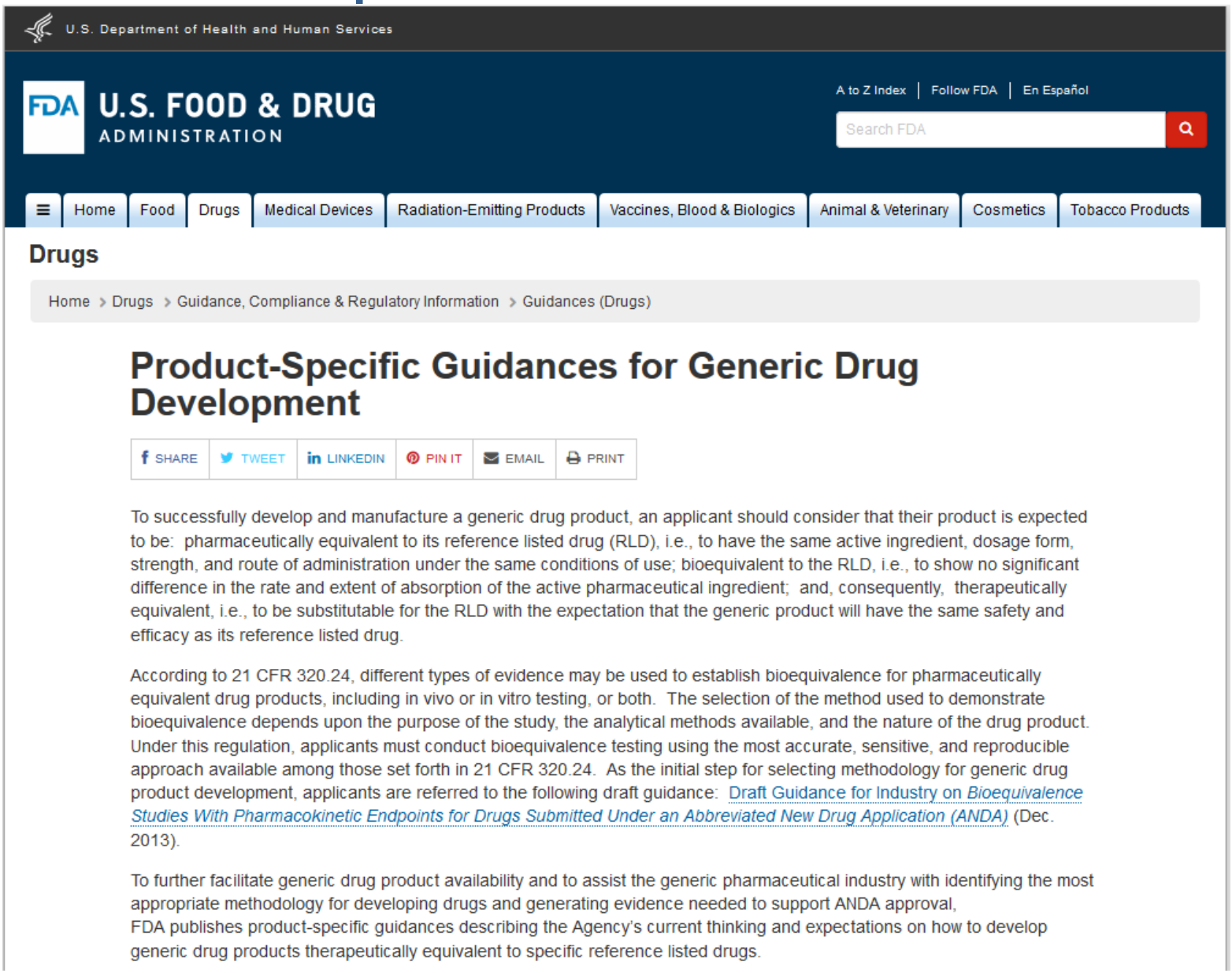
- Role of Product-Specific Guidances
- Recent PSG Postings:
  - Naloxone Hydrochloride Nasal Spray
  - Tiotropium Bromide Powder for Inhalation
  - Fluticasone Propionate Powder for Inhalation
- Conclusions

Product-Specific Guidances Facilitate Generic Drug Development

- Generics offer considerable savings to consumers
- $1.67 trillion saved over the last decade
- Development and posting of PSGs is a vital process
- Identify the Agency's current thinking on methodology for developing drugs
- Generate evidence needed to support generic approvals

https://blogs.fda.gov/fdavoice/index.php/2018/02/2017-was-another-record-setting-year-for-generic-drugs

Product-Specific Guidance Website



U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

A to Z Index | Follow FDA | En Español

Search FDA

Home | Food | Drugs | Medical Devices | Radiation-Emitting Products | Vaccines, Blood & Biologics | Animal & Veterinary | Cosmetics | Tobacco Products

Drugs

Home > Drugs > Guidance, Compliance & Regulatory Information > Guidances (Drugs)

Product-Specific Guidances for Generic Drug Development

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

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 referred to the following draft guidance: Draft Guidance for Industry on *Bioequivalence Studies With Pharmacokinetic Endpoints for Drugs Submitted Under an Abbreviated New Drug Application (ANDA)* (Dec. 2013).

To further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval, FDA publishes product-specific guidances describing the Agency's current thinking and expectations on how to develop generic drug products therapeutically equivalent to specific reference listed drugs.

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

PSGs for Generic Products

- Roles
  - To facilitate generic drug product availability
  - To assist generic pharmaceutical industry
  - To identify the most appropriate methodology to support ANDA
- Guiding Principles
  - 21 CFR 320.24
  - Different types of evidence may be used to establish bioequivalence (BE) for pharmaceutically equivalent drug products
  - Selection for BE method depends upon
    - Purpose of study
    - Analytical methods available
    - Nature of the drug product
  - Use the most accurate, sensitive, and reproducible approach available

https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm

Outline

- Role of Product-Specific Guidances
- Recent PSG Postings:
  - Naloxone Hydrochloride Nasal Spray
  - Tiotropium Bromide Powder for Inhalation
  - Fluticasone Propionate Powder for Inhalation
- Conclusions

Addressing the Opiate Crisis Remains an FDA Priority

"Unquestionably, our greatest immediate challenge is the problem of opioid abuse. This is a public health crisis of staggering human and economic proportion … we have an important role to play in reducing the rate of new abuse and in giving healthcare providers the tools to reduce exposure to opioids to only clearly appropriate patients, so we can also help reduce the new cases of addiction."

- Scott Gottlieb, FDA Commissioner
  Address to FDA staff, May 15, 2017

https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM601178.pdf

PSG: Naloxone Hydrochloride Nasal Spray

Contains Nonbinding Recommendations

Draft Guidance on Naloxone Hydrochloride

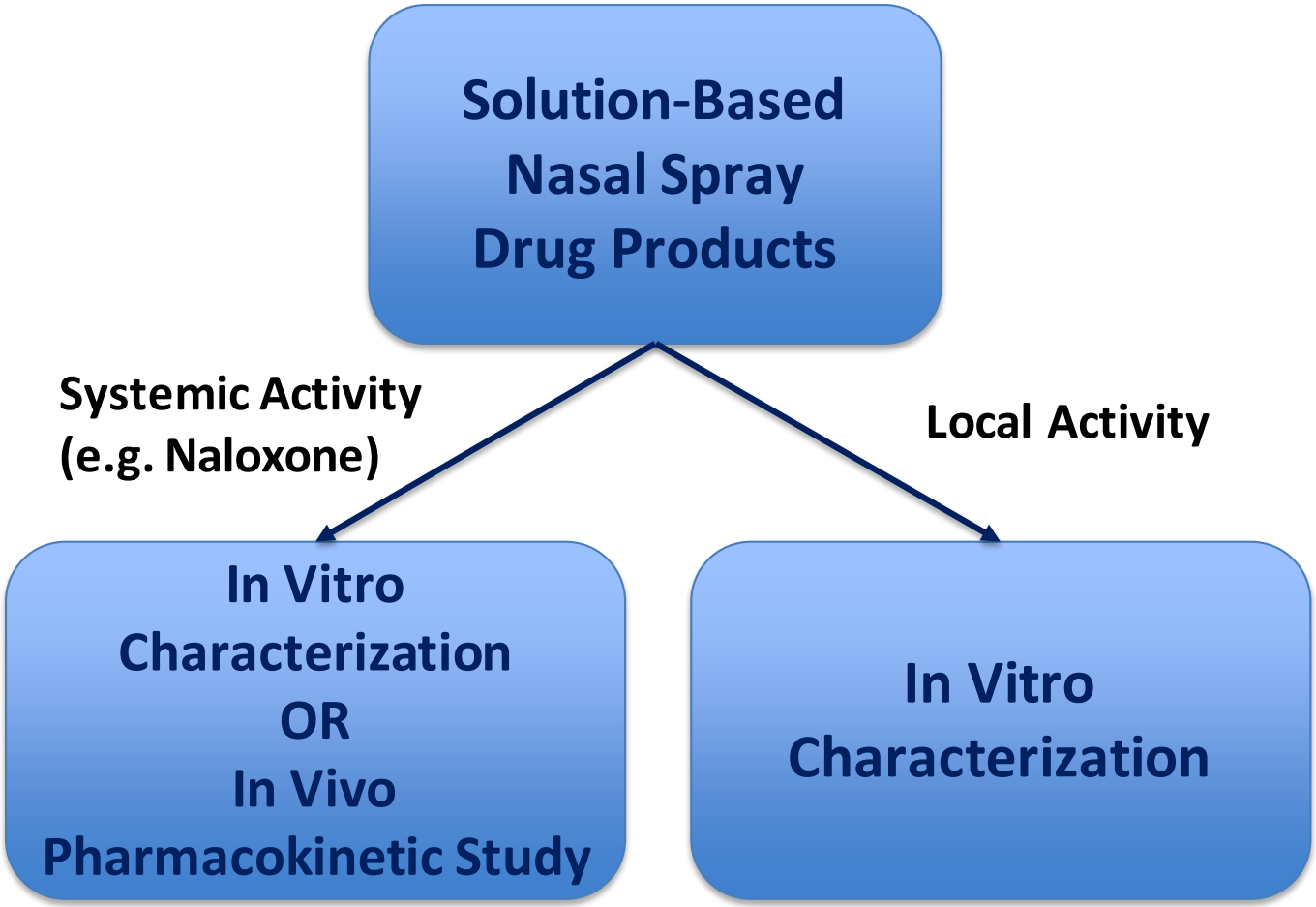
This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient:	Naloxone hydrochloride
Dosage Form; Route:	Spray; nasal
Strengths:	2 mg/spray 4 mg/spray
Recommended Studies:	Two options: In vivo or In vitro

Posted April, 2017

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM554404.pdf

Recommendations for Establishing Bioequivalence for Nasal Sprays



PSG: Naloxone Hydrochloride Nasal Spray

- In Vitro Studies Option
  - Rationale:
    - More sensitive to detect differences between formulations (if present)
    - Less variable than comparative clinical studies
    - Easier to control than comparative clinical studies
  - Requirements:
    - Qualitative (Q1) /Quantitative (Q2) Sameness in formulation
    - Device substitutability (e.g., pump and actuator design)

- In Vivo PK Study Option
  - Rationale:
    - Formulation differences may affect systemic exposure and performance

Naloxone Nasal Spray: In Vitro Option

- General design
  - Performed on 3 batches of Test and Reference (10 units/batch)
- Studies
  - **Single Actuation Content (SAC)-** Ensures equivalence in drug delivery over the product's labeled number of actuations
  - **Droplet Size Distribution by Laser Diffraction (LD)-** Important factor for determining where droplets deposit
  - **Drug in Small Particles/Droplets-** Determines drug content in size ranges capable of entering the lung (e.g., < 9.0 micron)
  - **Spray Pattern**
  - **Plume Geometry**
- Strengths:
  - 4 mg/spray and 2 mg/spray

Naloxone Nasal Spray: In Vivo Option

- General design
  - Single-dose, two-way, crossover fasting PK Study
  - Subjects: Healthy males and non-pregnant females, general population
  - Strength: 4 mg/spray x 1 spray (4 mg dose)
  - Equivalence (90% CI):
    - Based on AUC_{0_t}, AUC_{0_∞}, C_{max}
    - Supportive information: $pAUC_{0\_4min}$, $pAUC_{0\_10min}$, $pAUC_{10\_30min}$
      - Respiratory depression one of the main causes of death from opiate overdose
      - Reversing hypoxia/anoxia in the first few minutes is critical for limiting brain injury and overall survival
  - Waiver for the 2 mg/spray provided acceptable PK BE study, proportional similarity in formulation with 4 mg/spray

Naloxone Nasal Spray: Device

- User Interface Considerations (e.g. pump and actuator design)
- FDA's Draft Guidance *Comparative Analyses and Related Comparative Use Human Factor Studies for a Drug-Device Combination Product Submitted in an ANDA (January 2017)*
- Threshold Analyses
  - Labeling Comparison
  - Comparative Task Analysis
  - Physical Comparison of Delivery Device Constituent Part

https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm536959.pdf

Outline

- Role of Product-Specific Guidances
- Recent PSG Postings:
  - Naloxone Hydrochloride Nasal Spray
  - Tiotropium Bromide Powder for Inhalation
  - Fluticasone Propionate Powder for Inhalation
- Conclusions

COPD in the United States

- Chronic progressive disease caused by chronic inflammation and destruction of the airways and lung parenchyma
- Tobacco smoke is a key factor in developing COPD
- More than 15 million Americans diagnosed
- Patients often > 65 years of age
  - Likely to be on a fixed income
  - High cost of therapy can lead to skipped doses

https://www.cdc.gov/copd/index.html
https://www.npr.org/sections/health-shots/2017/06/02/529759280/many-copd-patients-struggle-to-pay-for-each-breath

COPD Treatments

- Spiriva HandiHaler® (Tiotropium Bromide) Powder for Inhalation
- Over $5 Billion in sales in 2014

- Generic competition for this product could provide significant cost savings for COPD patients

Stein, S., et al. *J Aerosol Med Pulm Drug Deliv.* 2017; 30(1): 20-41.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5278812/pdf/jamp.2016.1297.pdf

PSG: Tiotropium Bromide Inhalation Powder

Contains Nonbinding Recommendations

Draft Guidance on Tiotropium Bromide

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:	Tiotropium bromide
Dosage Form; Route:	Powder; inhalation
Strength:	EQ 0.018 mg base/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) dry powder inhalers (DPIs) containing tiotropium bromide.

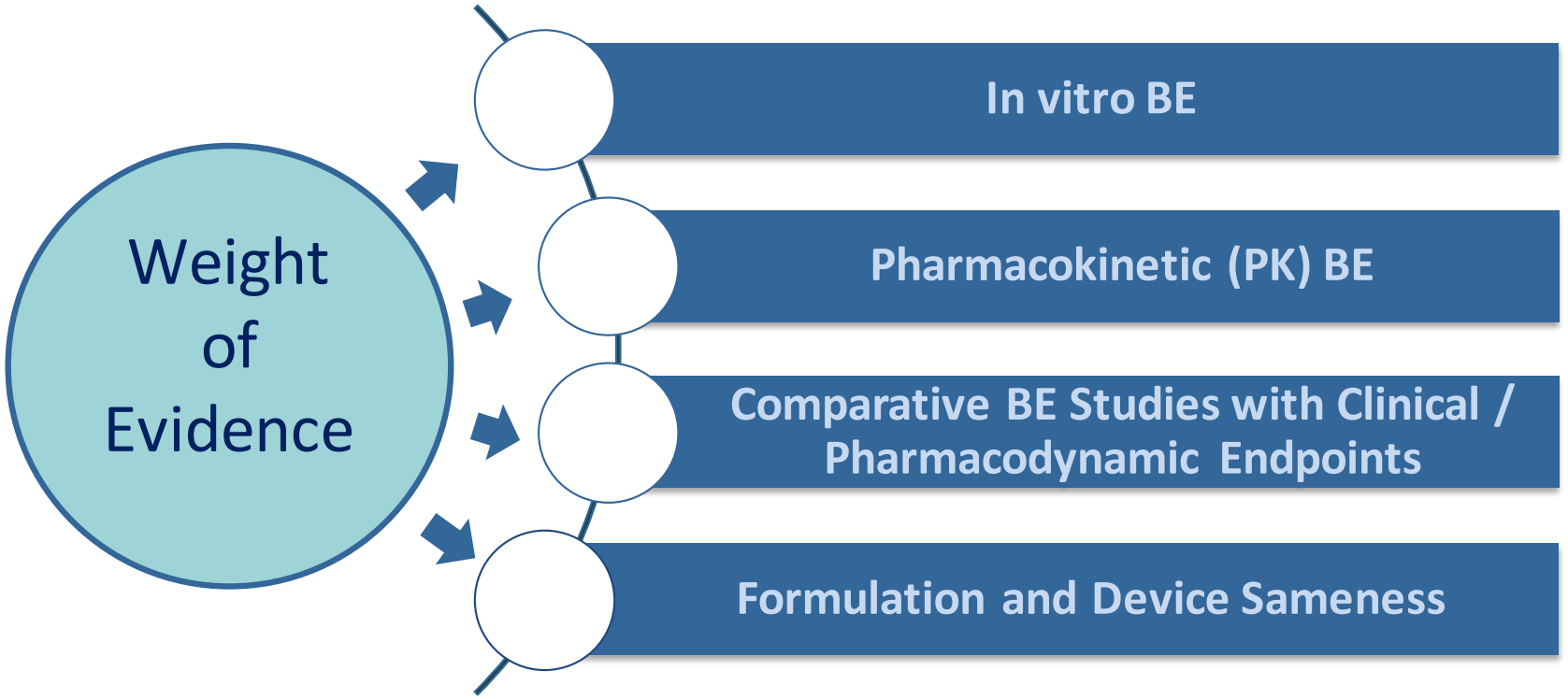
Posted October, 2017

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581192.pdf

Challenges in Developing Locally Acting Generic OINDPs

- Drug delivery is local to the site of action (e.g., lung tissue), not systemic
  - Intended target effect does not rely primarily on systemic absorption
  - Challenges to measuring local effect
- Device is integral part of the delivered dose
- Several factors influencing drug local and systemic bioavailability include:
  - Patient-device interactions
  - Device-formulation interactions
  - Regional drug distribution
  - Local dissolution/permeability/clearance

Weight of Evidence BE Approach



- Currently recommended for locally acting nasal suspensions, dry powder inhalers (DPIs) and metered dose inhalers (MDIs)
- Comparative clinical endpoint studies are long and costly, and least sensitive to formulation differences

Tiotropium Powder: In Vitro Studies

- General design
  - Performed on 3 batches of Test and Reference (10 units/batch)
- Studies
  - Single Actuation Content (SAC)
    - Ensures equivalence in drug delivery per inhalation at multiple stages of product life
    - Three flow rates (i.e., 20, 39, and 60 L/min) evaluated to ensure performance across the potential flow ranges used by patients of different ages and severity of disease
  - Aerodynamic Particle Size Distribution (APSD)
    - Believed to affect the total and regional deposition in the lung, and so critical to safety and performance
    - Evaluated using same flow rates used for SAC

Tiotropium Powder: In Vivo Studies

- Equivalence in Systemic Exposure
  - General Design
    - Single-dose, two-way crossover fasting PK BE study
    - Subjects: Healthy males and non-pregnant females, general population
    - Equivalence (90% CI): Based on AUC and C_{max}
  - Additional Comments
    - Subject training
    - Dose administration as per labeling (i.e., 2 inhalations from 1 capsule)
    - Bio-IND if dose exceeds maximum labeled single dose

Tiotropium Powder: In Vivo Studies

- Equivalence in Local Delivery
  - General Design
    - Randomized, single-dose, blinded (if possible), placebo-controlled, crossover or parallel, comparative clinical PD BE study
    - 2-week run-in period followed by one-day periods for each treatment
    - Subjects: Male/non-pregnant female COPD patients who meet inclusion/exclusion criteria, or ≥15% reversibility to bronchodilator treatment (justification should be provided)
    - Equivalence (90% CI): Based on baseline-adjusted FEV_1 $AUEC_{0\_24h}$

Tiotropium Powder: Formulation and Device

- Formulation
  - Q1/Q2 sameness recommended
  - If non-Q2, justification (e.g., in vitro testing of multiple drug-to-excipient ratios) should be provided
- Device
  - User Interface Considerations
    - Passive (breath-actuated) device
    - Pre-metered single-unit dose capsule-based format
    - Dose number
    - External operating principles and external critical design attributes
    - Size and shape
    - Device resistance
  - In vitro and in-use studies for functionality, accuracy and robustness
  - Threshold Analyses

Outline

- Role of Product-Specific Guidances
- Recent PSG Postings:
  - Naloxone Hydrochloride Nasal Spray
  - Tiotropium Bromide Powder for Inhalation
  - Fluticasone Propionate Powder for Inhalation
- Conclusions

Asthma in the United States

- Common, chronic disorder of the airways characterized by reversible airflow obstruction
- An estimated 39.5 million Americans have been diagnosed with asthma in their lifetimes
- Estimated medical costs related to asthma treatment were approximately $50 Billion

Asthma Facts. CDC's National Asthma Control Program Grantees. July 2013.
https://www.cdc.gov/asthma/pdfs/asthma_facts_program_grantees.pdf

Asthma Treatments

- Flovent Diskus® (Fluticasone Propionate) Powder for Inhalation
- Yearly costs between $1,800 and $2,400 in 2013

- Generic competition for this product could provide significant cost savings for asthma patients

Evaluating Inhaled Steroids Used to Treat: Asthma – Comparing Effectiveness, Safety, and Price. http://article.images.consumerreports.org/prod/content/dam/cro/news_articles/health/PDFs/InhaledSteroidsFINAL.pdf

PSG: Fluticasone Propionate Inhalation Powder

Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate

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:	Fluticasone propionate
Dosage Form; Route:	Powder; inhalation
Strengths:	0.05 mg/INH 0.1 mg/INH 0.25 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) dry powder inhalers (DPIs) containing fluticasone propionate.

Posted October, 2017

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581179.pdf

Fluticasone Powder: In Vitro Studies

- General design
  - Performed on 3 batches of Test and Reference (10 units/batch)
  - Strengths: 0.05 mg/Inh, 0.1 mg/Inh, 0.25 mg/Inh
- Studies
  - Single Actuation Content (SAC)
    - Ensures equivalence in drug delivery per across product life
    - Three flow rates (i.e., 30, 60, and 90 L/min)
  - Aerodynamic Particle Size Distribution (APSD)
    - Affects lung deposition, critical to safety and performance
    - Evaluated using same flow rates used for SAC

Fluticasone Powder: In Vivo Studies

- Equivalence in Systemic Exposure
  - General Design
    - Single-dose, two-way crossover fasting PK BE study
    - Subjects: Healthy males and non-pregnant females, general population
    - Equivalence (90% CI): Based on AUC and C_{max}
  - Strengths: 0.05 mg/Inh, 0.1 mg/Inh, 0.25 mg/Inh
  - Additional Comments
    - Subject training
    - Dose administration as per labeling (i.e., rinse mouth with water and spit out, do not swallow)
    - Bio-IND if dose exceeds maximum labeled single dose

Fluticasone Powder: In Vitro Studies

- Equivalence in Local Delivery
  - General Design
    - Randomized, multiple-dose, placebo-controlled, parallel, comparative clinical endpoint BE study
    - 2-week run-in period followed by 4-week treatment period
    - Strength: 0.05 mg/Inh
    - Subjects: Male/non-pregnant female asthma patients
      - Pre-bronchodilator FEV1 of ≥45% and ≤85% of predicted normal on screening/first treatment visit
      - Enrollment can include patients who meet the inclusion/exclusion criteria or enriched by using a patient subpopulation who respond well to the study treatment (justification should be included)
    - Equivalence (90% CI): Based on baseline-adjusted FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of the 4-week treatment

Fluticasone Powder: Formulation and Device

- Formulation
  - Q1/Q2 sameness recommended
  - If non-Q2, justification (e.g., drug-to-excipient ratio testing) should be provided
- Device
  - User Interface Considerations
    - Passive (breath-actuated) device
    - Pre-metered multi-dose format
    - Dose number
    - External operating principles and external critical design attributes
    - Size and shape
    - Device resistance
    - Dose indicator/counter
  - In vitro and in-use studies for functionality, accuracy and robustness
  - Threshold Analyses

Outline

- Role of Product-Specific Guidances
- Recent PSG Postings:
  - Naloxone Hydrochloride Nasal Spray
  - Tiotropium Bromide Powder for Inhalation
  - Fluticasone Propionate Powder for Inhalation
- Conclusions

Conclusions

- PSGs are a vital tool for generic product development
- PSGs communicate the Agency's current thinking on establishing equivalence between a test and reference drug product
- PSGs identify the most appropriate methodology to support an ANDA
- PSGs ultimately provide increased access to safe, affordable generic drugs
- The PSGs discussed today demonstrate the Agency's continued commitment to facilitating the development and approval of generics

Thank You!

- Acknowledgement
  - Kimberly Witzmann, M.D.
  - Renish Delvadia, Ph.D.
  - Denise Conti, Ph.D.
  - Markham Luke, M.D., Ph.D.
  - Robert Lionberger, Ph.D.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

QUESTIONS