New Tools for Generic OIDPs to Maximize Prospects of FDA Approval

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RDD

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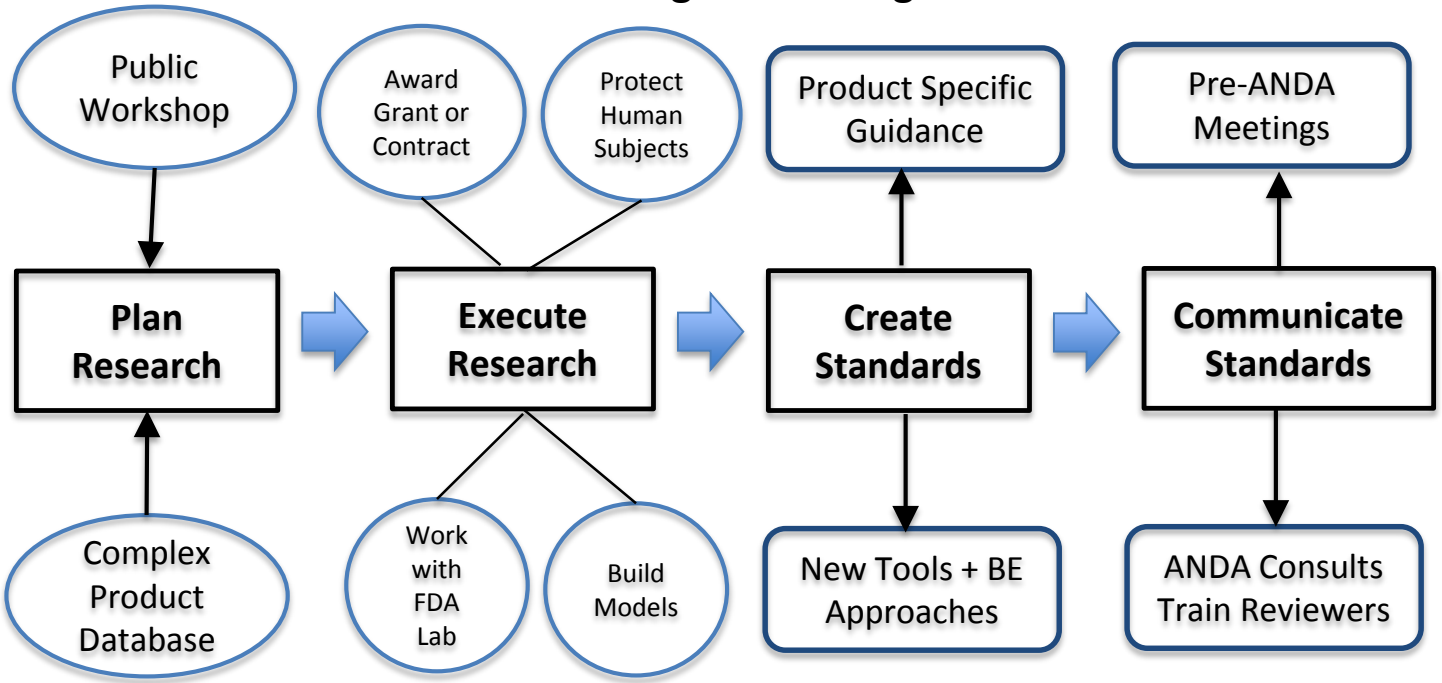
Tools for Generic Inhalation Products

- Almost no generic competition in the Orally Inhaled and Nasal Drug Product (OINDP) space
- Poster child for “complex generics”
  - In GDUFA II negotiations
  - In the FDA Commissioners Drug Competition Action Plan (DCAP)
- OGD has built new tools
  - Scientific Tools (Research Results)
  - Regulatory Tools (Guidance, pre-ANDA meetings)

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**



Pre-GUDFA I Landscape for Generic OINDP

- Almost no generic competition in the inhalation space
- No bioequivalence guidance for inhalation products
- FDA research underway
  - eNO as endpoint for locally delivery
  - Critical Material Attributes of inhalation products

Current Generic Landscape of OINDP

- 68 approved OINDPs
  - ~50 generic nasal products approved (~15 reference products)
  - No generics approved for MDI or DPI orally-inhaled products
- 39 PSGs were issued since 2013
  - 57% of the approved OINDPs
  - Both in vitro BE only option and a weight of evidence approaches were recommended based on product-specific attributes

13 PSGs (Nasal)	**Current PSGs have in vitro only BE option (for Q1/Q2 the same products)**
26 PSGs (Nasal and Inhaled)	**Current PSGs recommend weight of evidence approach**

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

GDUFA Regulatory Science Initiatives for OINDPs

- Identification of formulation and device variables which are important for successful development of generic OINDPs

- Development of clinically relevant in vitro and in silico tools and methodologies for prediction of in vivo regional drug deposition and dissolution from OINDPs, and to assess their applicability in generic OINDPs development programs

- Identification, validation and standardization of novel techniques that may have the potential to reduce the burden of current BE requirements for generic OINDPs.

Research Overview

- For a deep dive
  - New Insights for Product Development and Bioequivalence Assessments of Generic Orally Inhaled and Nasal Drug Products
    - January 9, 2018 (8:30 a.m. – 4:30 p.m.), FDA White Oak Campus
    - https://www.fda.gov/Drugs/NewsEvents/ucm576064.htm
    - Recording is available
- Today I will summarize

Research Origins

- Early work: Robert Price and Jag Shur
  - Particle characteristics are critical
- Build out tools that would measure this impact
  - CFD (for lungs and for device)
  - Dissolution
  - Realistic mouth-throat models
- Explore use of systemic PK for BE
  - Conduct in vivo PK study of different formulations
  - Build PBPK models of the lung to aid deconvolution

Research Projects

Formulation

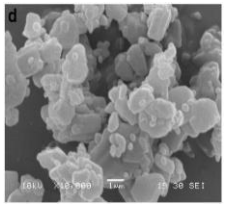
Human Factors

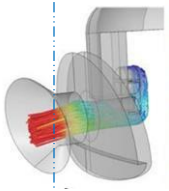
Dissolution

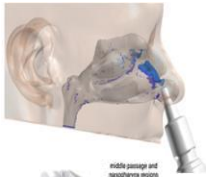
Device

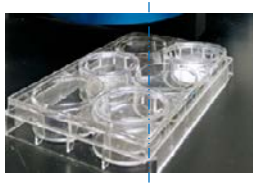
Regional Deposition

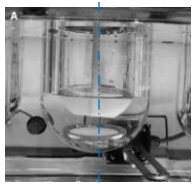
Absorption











Computational Modeling in OINDP Development

- Combination of CFD and PBPK to predict deposition, dissolution, and absorption
  - Impact of in vitro parameters on deposition and absorption
  - Effects of disease state on deposition and absorption
  - Method for predicting mucociliary clearance simultaneously with dissolution and absorption
- A well validated model can answer questions relevant to regulatory decision-making that are difficult to answer with currently available in vitro or in vivo techniques
  - Regional deposition of aerosolized drug within individual branches/lobes of the airway
  - Prediction of local bioavailability and its relationship with systemic pharmacokinetics

CFD Predictions of Aerosol Transport and Deposition

- Physics-based modeling framework capable of predicting regional deposition of OINDP aerosols
- Differences in formulation and device design may be predicted, as well as their impact on regional deposition
- Variability due to orientations, breathing patterns and anatomical differences may be examined

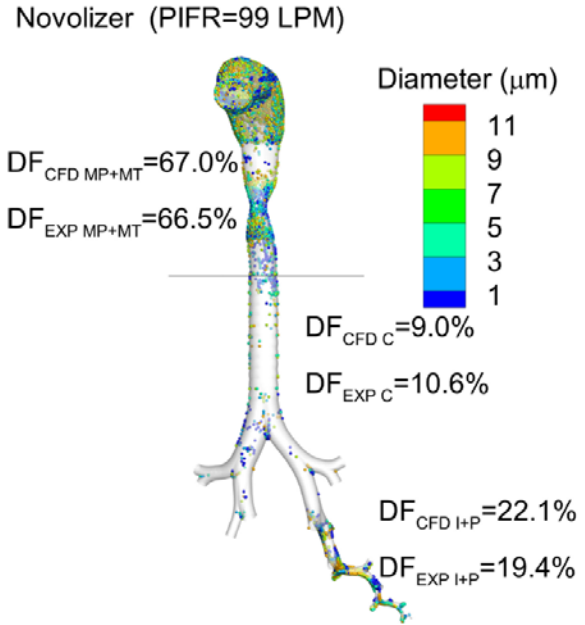
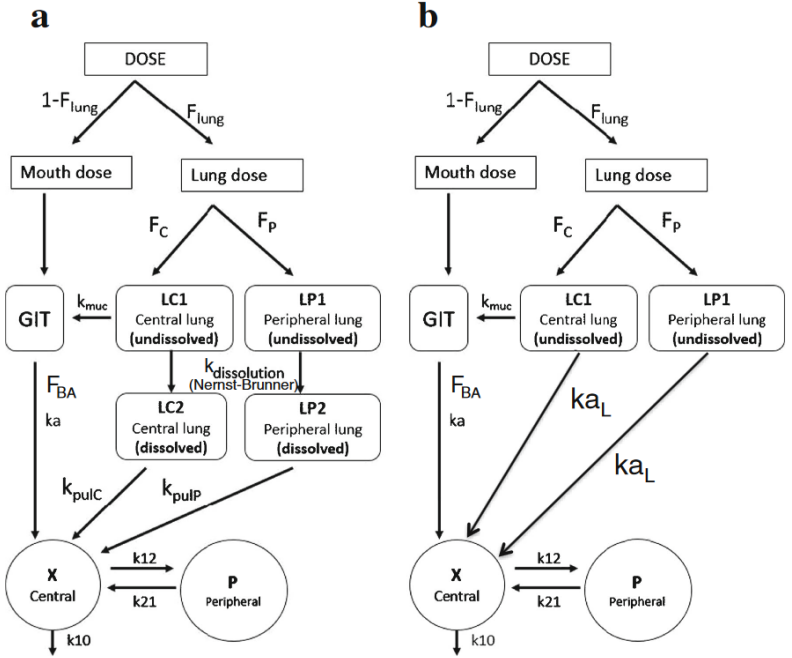


Figure 6 from Tian et al. (2015), showing of CFD predictions of deposition fraction (DF) in human airway model for Novolizer dry powder inhaler, as compared with in vivo data from Newman et al. (2000)

1. Tian G, Hindle M, Lee S, Longest PW. Validating CFD predictions of pharmaceutical aerosol deposition with in vivo data. Pharmaceutical research. 2015;32(10):3170-87.
2. Newman SP, Pitcairn GR, Hirst PH, Bacon RE, O'Keefe E, Reiners M, Hermann R. Scintigraphic comparison of budesonide deposition from two dry powder inhalers. European Respiratory Journal. 2000;16(1):178-83.

PBPK Predictions of OINDP Absorption

- Compartmental modeling approach used to predict dissolution and absorption of deposited drug particles
- Combination of CFD and PBPK can predict local and systemic absorption
- Useful for determining the extent that in vitro testing is indicative of local and systemic delivery, and for identifying appropriate bioequivalence limits on in vitro parameters



Compartmental model schemes for dry powder inhaler drug delivery from Bhagwat et al. (2017)

3. Bhagwat S, Schilling U, Chen MJ, Wei X, Delvadia R, Absar M, Saluja B, Hochhaus G. Predicting Pulmonary Pharmacokinetics from In Vitro Properties of Dry Powder Inhalers. Pharmaceutical research. 2017 (in press).

Dissolution Methods for OINDPs

- Predictive in vitro drug dissolution tests may provide a link between regional drug deposition and local/systemic pharmacokinetics for OINDPs containing poorly soluble drugs
- Bio-predictive dissolution tests may provide insight about potential in vivo performance variability of RLD and generic test products, and reduce the likelihood of comparative clinical study failures during BE determinations

But…

- Dissolution for inhalation is not well-established

Therefore…

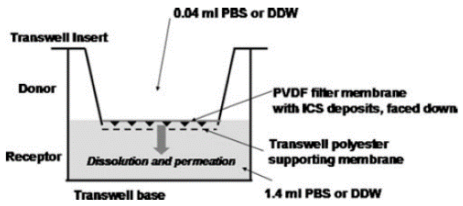
- FDA funded three different groups in this area

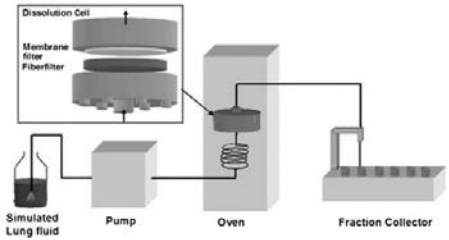
Key Challenges with Development of Dissolution Methods for OINDPs

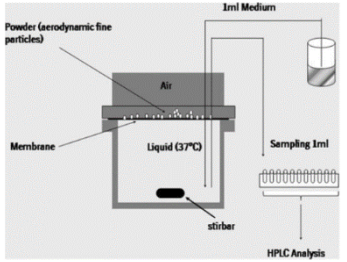
- Sample collection
- Method for transferring collected samples to dissolution apparatus
- Sink condition vs. low volume physiologically relevant conditions
- Number of dissolution media
- Validation/bio-predictability
- Acceptance criteria
- Standardization of the method

Dissolution Results

- Three grants (Bath, VCU, UFlorida) evaluated different approaches to OINDP dissolution
- Wealth of data on
  - Sample Collection, Apparatus, Medium, Validation, Correlation with PK





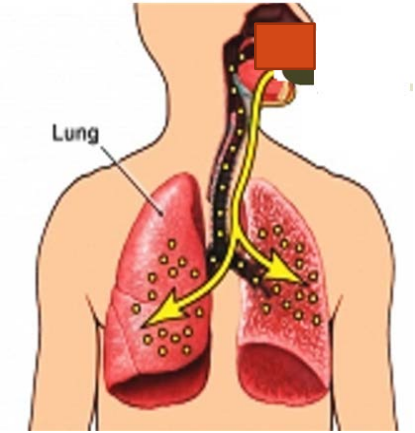


Realistic in Vitro Tests for OIDNPs?

- Current in vitro methods are designed for quality control purpose and may have limited predictability of drug deposition in vivo because they do not adequately mimic
  - airway geometry
  - actual use conditions (breathing/inhalation profile, orientation etc)
- 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
- Would be a great tool for formulation development and could support test to reference comparisons

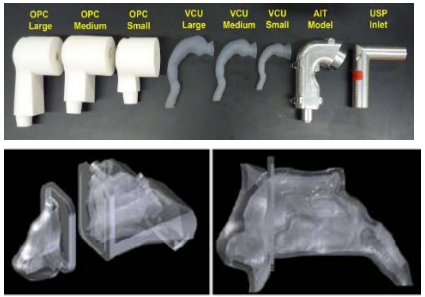
Realistic in Vitro Methods

- Model in vivo deposition



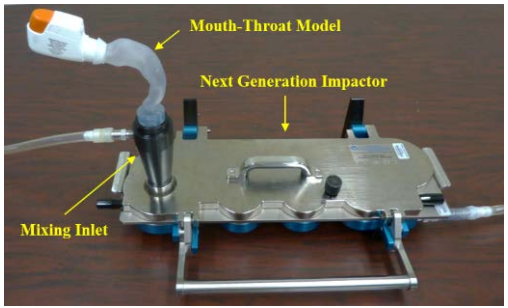
http://images.lifescript.com/images/ebsco/images/inhaled_poison.jpg

- Representative Physical Models



- Patient use conditions
  - Inhalation profiles

- Combine in new in vitro test

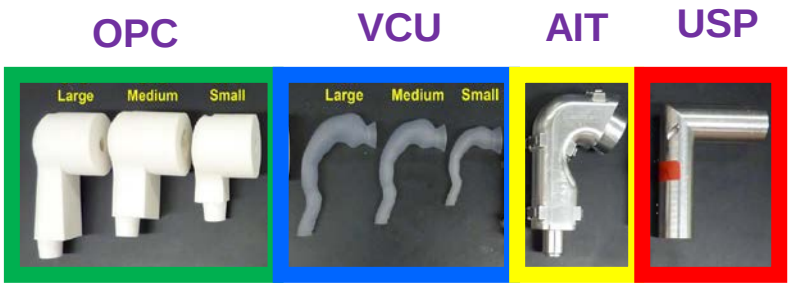


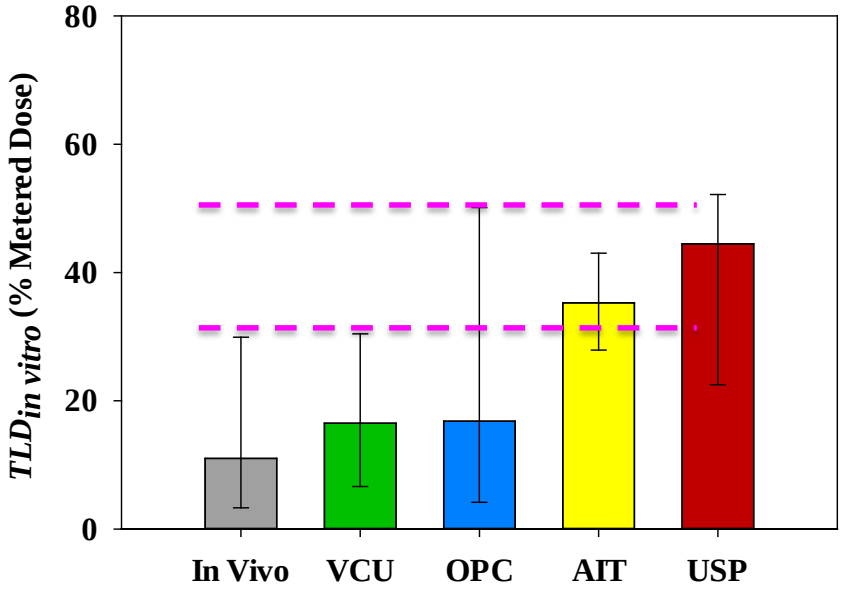
Research Grant #1U01FD005231-01 described at
https://www.fda.gov/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/ucm592245.htm

Research Outcomes

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

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





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New Research Projects in FY 17

- Investigating the Microstructure of Dry Powder Inhalers using Orthogonal Analytical Approaches (University of Bath)

- Investigating Orthogonal Analytical Approaches to Demonstrate Bioequivalence of Nasal Suspension Formulations (University of Bath)

- Patient's Perception of Dry Powder Inhaler Airflow Resistance (Imperial College of London)

2018 Research Priorities for OINDPs

- Improve Physiologically Based Pharmacokinetic (PBPK) models of drug absorption via complex routes of delivery
- Develop more efficient alternatives to the use of forced expiratory volume in one second (FEV1) clinical endpoint BE studies for inhaled corticosteroids
- Develop alternatives to clinical endpoint BE studies for locally-acting nasal products
- Evaluate the impact of identified differences in the user-interface on the substitutability of generic drug-device combination products

GDUFA Regulatory Science Priorities for Fiscal Year 2018;
https://www.fda.gov/downloads/Drugs/ResourcesForYou/Consumers/BuyingUsingMedicineSafely/GenericDrugs/UCM582777.pdf

Research Summary

- 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
  - **43 Peer Reviewed Publications**
  - **35 Presentations at Scientific Meetings**
- Regulatory science research informs PSGs, and helps provide expectations for how to develop generic drug products that are therapeutically equivalent to their RLDs
  - **39 Product Specific Guidances**
- 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

For More Information

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

Pre-ANDA Interactions with FDA: 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

Complex Drug Products In GDUFA II

- Complex active ingredients- peptides, polymeric compounds, complex mixtures of APIs, naturally sourced ingredients
- Complex formulations/dosage forms- liposomes, colloids, transdermals, long-acting injectables
- Complex routes of delivery- locally acting drugs such as dermatological, complex ophthalmological and otic products
- Complex drug-device combination products- metered nasal sprays, metered dose inhalers, auto-injectors
- Other products where complexity or uncertainty concerning the approval pathway or possible alternative approach would benefit from early scientific engagement

GDUFA II commitment letter.
http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf

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

GDUFA II Pre-ANDA Program

- New meetings to accelerate access to generics of complex products
  - Product development meeting
  - Pre-submission meetings
  - Mid-review-cycle meetings

Product Development Meeting Goals

- Scientific exchange on specific issues (e.g., a proposed study design) or questions
- Targeted advice from FDA for an ongoing ANDA development program

Eligibility

- FDA will grant Product Development Meetings if
  - The request concerns development of a complex product for which
    - FDA has not issued a product specific guidance or
    - The applicant proposes an alternative bioequivalence method of a different class
  - The request contains a complete meeting package including data and specific proposals
  - A controlled correspondence would not adequately address the questions
  - The meeting would significantly improve ANDA review efficiency

Meeting Request Submission

- Obtain a pre-assigned ANDA number before requesting the meeting
- Use CDER Direct NextGen Collaboration Portal (the Portal) to submit the meeting request

Meeting Package Content

- Provide clear and specific questions about your development program
- Include data supporting the proposed new approach that may include
  - Characterization of the RLD and ANDA products
  - Results from pilot studies
  - Comparisons of the proposed approach to that currently recommended by FDA

FDA Staff Roles

- Division Level Signer
  - An ORS division director or deputy who makes the decision to grant and oversees the meeting process
  - Accountable for the accuracy and completeness of the response
- Meeting Project Manager
  - Point of contact for industry
  - Facilitates internal meeting preparation, consults and information sharing
- Meeting Team Leader
  - Responsible for coordinating all discipline reviews into a consistent response

Meeting Request Evaluation

- FDA will evaluate the meeting request
- Within 30 days (year one and two) or 14 days FDA will grant or deny the meeting
- After granting, FDA will offer a meeting date within 120 calendar days of granting the request

Meeting Package Review

- ORS project manager will be your point of contact
- FDA staff will review the meeting package, consult if needed and send information requests
- GDUFA research prepares FDA staff for these evaluations
- Respond to IRs via the Portal

Before Meeting Day

- 5 days before the meeting you will receive preliminary written comments from FDA
  - Use these to optimize your meeting agenda
- Submit your meeting slides and agenda via the Portal

Meeting Day

- Meeting participants discuss the questions and the data provided to assist the prospective ANDA applicant's complex product development program
- FDA cannot review new material presented at the meeting for the first time

Post-Meeting

- FDA will issue official minutes within 30 days of the meeting
- If you would like FDA to consider your meeting summary
  - Submit it via the portal within 7 days of the meeting

Pre-Submission Meeting Goals

- Provide an opportunity for the applicant discuss and explain content and format of the ANDA to be submitted
- Provide an opportunity to give advice that will enable efficient review and improve the chance of first cycle approval
  - Identify items or information for clarification before submission
- Allow FDA to share information from product development meetings with the ANDA review team and prepare for unique review issues

Eligibility

- FDA will generally grant Pre-Submission Meetings
  - If you were granted a Product Development meeting after October 1, 2014
- FDA may grant Pre-Submission Meetings
  - if in FDA's judgment the pre-submission meeting would improve review efficiency

Meeting Request Submission

- Obtain a pre-assigned ANDA number before requesting the meeting
- Use CDER Direct NextGen Collaboration Portal (the Portal) to submit the meeting request

Meeting Package Content

- Outline the unique, novel or complex aspects of your upcoming submission that you will present at the meeting
- If you have specific questions, provide appropriate background material and data related to those questions

Meeting Evaluation

- FDA will evaluate the meeting request
- Within 30 days (year one and two) or 14 days FDA will grant or deny the meeting
- After granting, FDA will offer a meeting date with in 120 calendar days of granting the request

Meeting Package Review

- ORS project manager will be your point of contact
- FDA will identify representatives of the ANDA review team to participate in the pre-submission meeting. Emerging technologies will include Office of Pharmaceutical Quality Emerging Technology Team.
- FDA will communicate the results of the product development meeting or other pre-ANDA interactions to the review team
- FDA staff will review the question in the meeting package, consult if needed and send information requests
- Respond to IRs via the Portal

Before Meeting Day

- If you asked specific questions, 5 days before the meeting you will receive preliminary written comments from FDA
  - Use these to optimize your meeting agenda
- Submit your meeting slides and agenda via the Portal

Meeting Day

- FDA staff listens to your presentation of the unique, novel or complex aspects of your upcoming submission
- FDA staff advises you on how to present the information in your submission to support an efficient review and increase the potential of a first cycle approval
- FDA staff discusses our written responses to questions
- FDA will not provide a substantive review of summary data or full study reports

Post-Meeting

- FDA will issue official minutes within 30 days of the meeting
- If you would like FDA to consider your meeting summary
  - Submit it via the portal within 7 days of the meeting

Mid-Review-Cycle Meetings

- If you had a pre-ANDA meeting on a complex product and use the same pre-assigned ANDA number to submit an ANDA
- After you submit your ANDA the RPM will contact you to arrange a mid-review-cycle teleconference with the FDA staff reviewing your application

How to Use the Pre-ANDA Process Effectively

- FDA's current experience is that inhalation ANDAs have a large number of first cycle deficiencies
  - Read our general guidance on inhalation products
  - Read our Product Specific Guidance on inhalation products
  - Use controlled correspondence to ask specific questions about general or product specific guidance
  - Use Product Development Meeting if you propose something different than in the PSG
  - Use Pre-submission meeting to make the review more efficient

MDI/DPI Quality Guidance

- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products – Quality Considerations Draft Guidance for Industry
  - April 18, 2018
    - https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070573.pdf

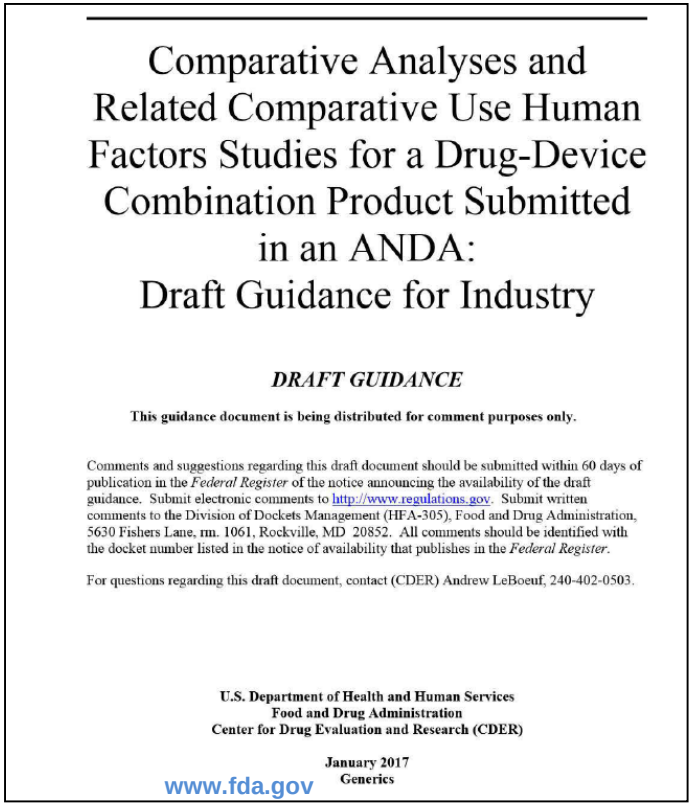
Feedback on Innovative BE Approaches

- GDUFA II Pre-ANDA product development meetings for complex products allows FDA to engage with industry to support innovative and efficient methods to demonstrate equivalence
  - new development strategies when no PSG is available
  - development of alternative development (i.e., change in study type, such as in vitro to clinical) for a complex product for which FDA has issued a product-specific guidance
- The pre-ANDA program is designed to accelerate access to generic versions of complex products, including OINDPs.
- A complete meeting package containing clear and specific questions that are supported by appropriate data.

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM578366.pdf

Generic Inhalation Products are Drug-Device Combination Products

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

www.fda.gov

- Use the controlled correspondence process for early feedback on patient use issues
- Use the meeting process if human factors studies may be part of your submission

How to use the Pre-ANDA Process Effectively

- Order of interactions with FDA
  - Industry should pay careful attention to the research results that have been published as they provided significant insight into key product characteristics needed to ensure equivalence.
  - Prototype generic device first
    - Identify any user interface issues
  - In vitro characterization of RLD batches and potential ANDA products

How to use the Pre-ANDA Process Effectively

- Order of interactions with FDA
  - PK study
    - Batch to batch variability?
  - Design clinical end-point study or discuss alternative approach
    - Product Development Meeting for alternative approach
    - Controlled Correspondence for protocol questions if there is a PSG
    - Product Development Meeting if there is no PSG

How to use the Pre-ANDA Process Effectively

- Order of interactions with FDA
  - Use the pre-submission meeting to improve first cycle approval rate
  - Use the pre-submission meeting to ask how to present novel aspects of your ANDA for review

Acknowledgements

Current ORS Staff

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