Considerations for Pre-ANDA Meeting Requests for Orally Inhaled and Nasal Drug Products

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Outline

- Addressing generic development challenges for orally inhaled and nasal drug products (OINDPs)
- Types of pre-Abbreviated New Drug Application (pre-ANDA) meeting requests
- Common types of requests in product-development (PDEV) meetings
  - Product-specific guidance (PSG) posted vs no PSG posted, alternative bioequivalence (BE) approach, alternative study design
- Recommended information to be submitted

Addressing the Challenges in Developing BE Locally Acting Generic OINDPs

- Developing generics for OINDP is challenging because of the multiple factors that can influence drug delivery to the site of action
- To facilitate the development programs for OINDP generics, FDA provides assistance and communicates its recommendations for establishing bioequivalence (BE) through several methods, including:
  - Posting of product-specific guidances (PSGs)
  - Answering controlled correspondences (CCs)
  - Conducting formal meetings with the generic industry through the Pre-ANDA Meeting Request process

Types of Pre-ANDA Meetings for Complex Products

- Product Development (PDEV)
  - Provide for discussion of specific scientific issues or questions (e.g., a proposed study design, alternative approach, or additional study expectations), in which FDA will provide targeted advice regarding an ongoing ANDA development program
- Pre-Submission (PSUB)
  - Provide an opportunity for prospective ANDA applicants to discuss and explain the format and content of the ANDA to be submitted (e.g., data to support equivalence claims, types of data that will be contained in the ANDA)

Guidance for Industry: Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA (Oct 2017): https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf

Common Types of Requests in PDEV Pre-ANDA Meetings Received for OINDPs

- There is a PSG
  - Evaluation of proposed **alternative** approach for bioequivalence
  - Evaluation of proposed study design that deviate from the PSG
  - Multiple questions or complex issues not covered by the PSG

- There is not a PSG
  - Evaluation of **proposed approach** for bioequivalence

Research Initiatives for OINDPs

- Identification of formulation and device variables
- Development of clinically relevant in vitro methods for prediction of in vivo drug deposition and dissolution
- Development of computational fluid dynamic (CFD) and physiology-based pharmacokinetic (PBPK) models for prediction of the fate of drugs
- Identification, validation, and standardization of novel techniques that may have the potential to reduce the burden of current BE requirements

GDUFA Regulatory Science: https://www.fda.gov/industry/generic-drug-user-fee-amendments/gdufa-regulatory-science
Science & Research: https://www.fda.gov/drugs/generic-drugs/science-research

ORS Research Activities for OINDPs

Formulation

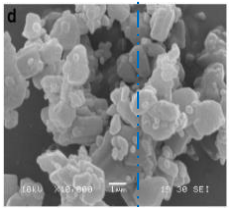
User Interface

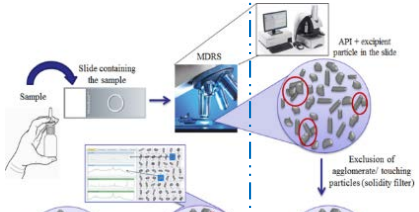
Dissolution

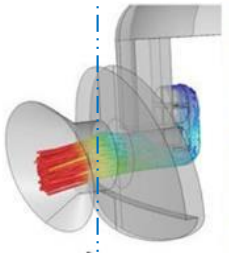
Device

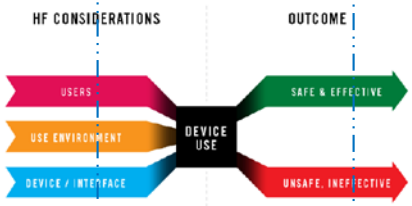
Regional Deposition

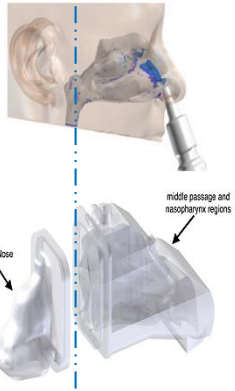
Absorption

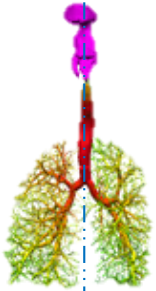


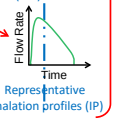


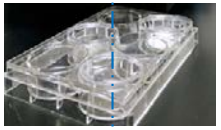


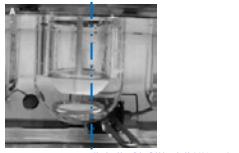




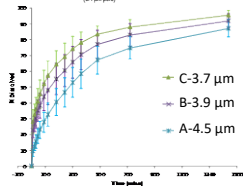


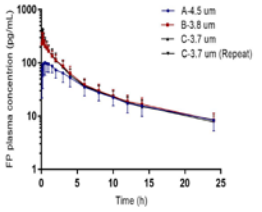






In vitro APSD test more predictive of in vivo deposition





Proposed Approaches for Bioequivalence (w/wo PSG)

- Clearly defined and explained in detail
- Supported by scientific rationale, clear and concise justification
- Supported by preliminary data (if available) and/or literature
- If there is a PSG:
  - How challenges in establishing bioequivalence will be addressed?
  - If requesting not to conduct a comparative clinical study, what additional studies are proposed? What is the relevance for bioequivalence in the context of the proposed approach?

PSGs:

- *Use the most accurate, sensitive, and reproducible approach available*
- *Identify the current thinking methodology to support ANDA*

Proposed T Formulations (Q1/Q2)

- FDA assessment
  - Q1 means the test (T) formulation uses the same excipients as the reference (R) formulation
  - Q2 means that the concentration of excipients used in the T formulation are within +/- 5% of those used in the R formulation

- Information to submit
  - Up to 3 proposed T formulations per each strength
  - Complete information about all excipients (e.g., names, grades, hydrate or anhydrous)
  - Concentration (e.g., %w/w, %w/v) of excipients inside the container (e.g., canister, bottle, blister, capsule, reservoir)

Note: *Q1/Q2 questions may be submitted as standard CC (60-day clock)*

Proposed T Device (User Interface)

- FDA assessment
  - Comparative (threshold) analyses as per the FDA guidance, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA* (Jan 2017)
    - Labeling comparison
    - Comparative task analysis
    - Physical comparison of the delivery device constituent part
- Information to submit
  - Samples of T and R devices
  - Comparative (threshold) analyses per guidance above
  - Specific question(s) based on the outcomes of comparative analyses

***Note**: Device (user interface) questions may be submitted as standard CC (60-day clock), but it may be converted to complex CC (120-day clock)*

Proposed BE Comparative Clinical Study Protocol

- BE comparative clinical study protocols are not pre-reviewed
  - Acceptability is determined during the scientific review of the ANDA
- Ask specific, detailed questions on complex issues, for example:
  - Study design (crossover vs parallel)
  - Study population (alternative or enriched with better responders)
  - Statistical analysis (ANCOVA with specific covariate(s))
  - Endpoints (AUC vs pAUC, assessment at 2 weeks vs 4 weeks of treatment)
- Provide scientific rationale, clear and concise justification
- Provide pilot/preliminary data (if available) and/or literature

Note: *In some instances, a complex CC (120-day clock) may be considered*

Proposed "Biowaiver" of In Vivo Studies

- FDA assessment
  - In general, in vivo bioavailability or bioequivalence of complex OINDPs may not be self-evident, so that a request to simply "waive" in vivo studies based on 21 CFR 320.22 may not be applicable
  - Product-specific
  - Case-by-case manner
  - Ultimately determined at the time of ANDA submission

- Information to submit
  - Alternative approach for BE
    - Rationale and justification for the proposal
    - Preliminary data, if available, and/or literature

Is this Acceptable?

- Examples
  - Is the ANDA acceptable for filing?
  - Is the ANDA acceptable for review?
  - Will the ANDA be approved?

- These types of vague, non-specific questions cannot be adequately addressed through pre-ANDA meetings
  - Scientific review of ANDA is time- and resource-intensive
  - Acceptability for filing and approvability depend on many factors, which may not be apparent until after all data has been reviewed
  - Requires involvement of multiple disciplines/offices/centers within FDA
- Ask specific, detailed questions about complex situations or issues for your generic development program

Takeaways

- OINDPs are complex drug-device combination products with multiple factors that can influence drug delivery to the sites of action
- FDA facilitates OINDP generic development through PSGs, CCs and Pre-ANDA Meeting Requests with the industry
- Considerations for pre-ANDA meeting requests
  - Meeting type (PDEV vs PSUB)
  - For PDEV meetings:
    - Proposed alternative approach for BE
    - Proposed study design that deviate from the PSG
    - Multiple questions or complex issues not covered by the PSG
    - Focus on complex situations or issues for the development program
    - Supported by scientific rationale, clear and concise justification
    - Supported by preliminary data, if available, and/or literature

Questions ?

- General Guidances
  - Pre-ANDA Meetings
    - *Formal meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA* (Oct 2017):
    - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm578366.pdf
  - Controlled Correspondences
    - *Controlled Correspondence Related to Generic Drug Development* (Nov 2017):
    - https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf

- Email: PreANDAHelp@fda.hhs.gov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ADMINISTRATION

Orally Inhaled and Nasal Drug Products (OINDPs)

- Drug-device combination products
- Treatment of diseases of respiratory tract
  - Asthma, chronic obstructive pulmonary disease (COPD), rhinitis
- Complex products*
  - Formulations, routes of delivery, dosage forms

* As per GDUFA II Commitment Letter: https://www.fda.gov/downloads/forindustry/userfees/genericdruguserfees/ucm525234.pdf

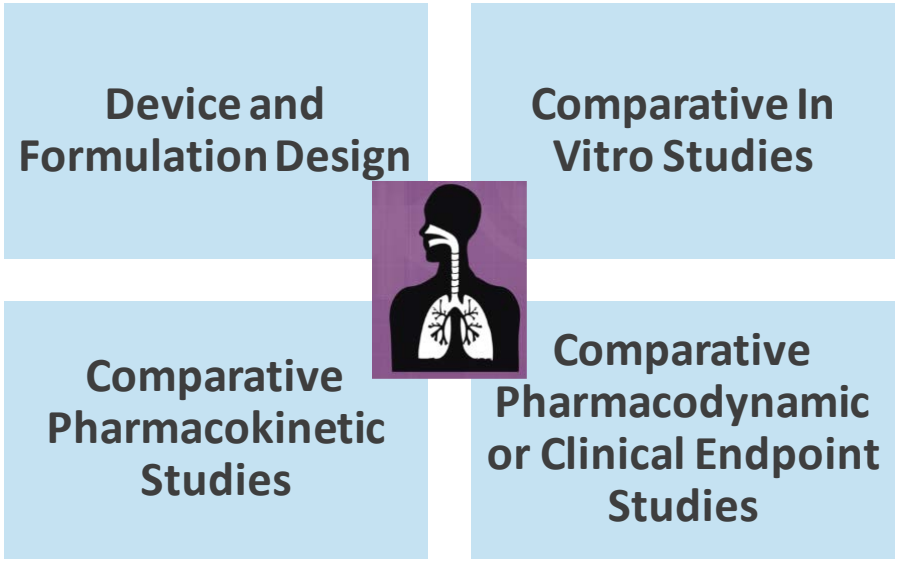
Complexity of OINDPs

Drug State	Site of Action	Dosage Form	Route
Solution	Systemic	Aqueous Spray	Nasal
	Local	Aerosol Metered	Nasal
			Inhalation
		Aqueous Spray	Nasal
			Inhalation
Suspension	Local	Aqueous Spray	Nasal
		Aerosol Metered	Inhalation
Solid blend	Systemic	Powder	Nasal
			Inhalation
	Local	Powder	Inhalation

Challenges in Developing BE Locally Acting Generic OINDPs

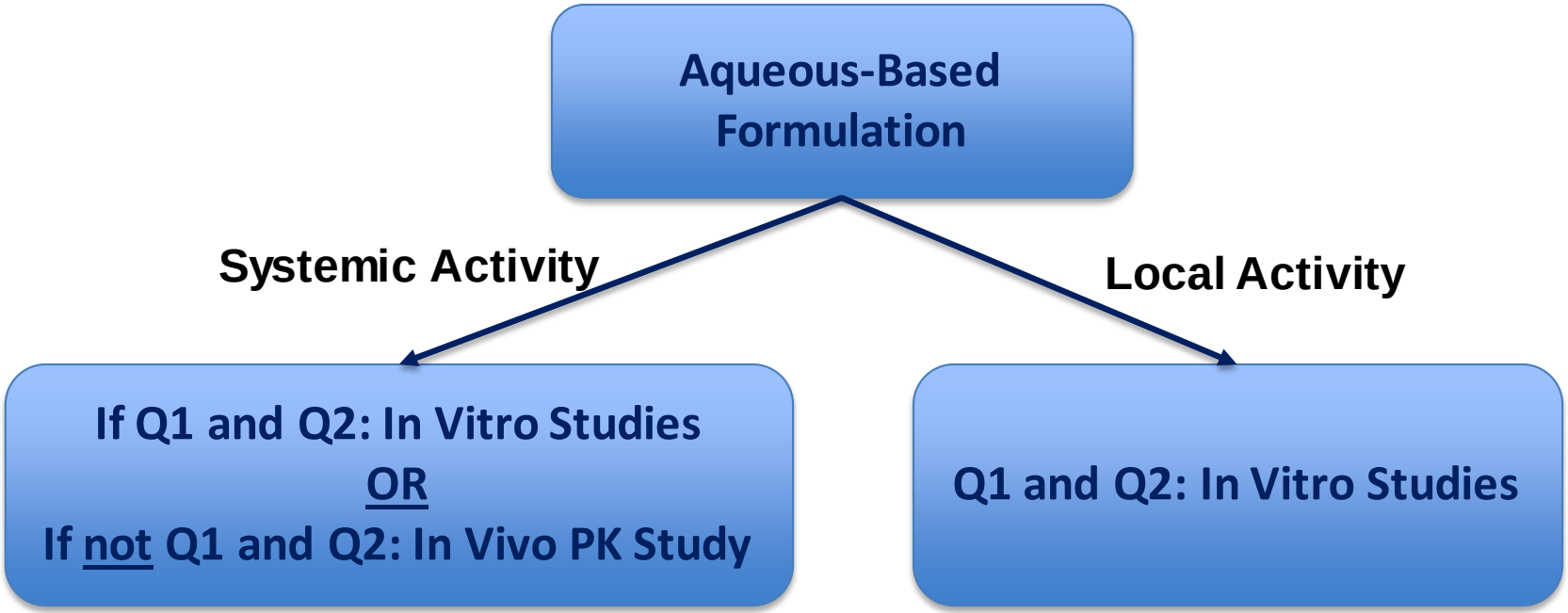
- Device plays an essential role in delivering the dose
- Several factors influencing drug bioavailability
  - Patient-device interactions (e.g., patient effort for inhalation)
  - Device-formulation interactions
  - Regional drug distribution
  - Local dissolution/permeability/clearance
- Drug delivery is local to the site of action (e.g., lung tissue or nasal cavity), not systemic
  - Intended target effect does not rely primarily on systemic absorption
  - Challenges to measuring local effect

Weight of Evidence Approach for Establishing BE for OINDPs



- Currently recommended for **locally acting** dry powder inhalers (DPIs), metered dose inhalers (MDIs) and nasal suspension sprays
- Incomplete understanding of the relevance of results from in vitro and in vivo PK BE studies to drug concentrations at local site of action
- Uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE

Recommended BE Approach for Nasal Solution Spray Products



Pre-ANDA Communications 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 (PSGs)
  - https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm
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