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Addressing the Challenges with Orally Inhaled and Nasal Drug Products (OINDPs) Through the Pre-ANDA Meeting Process

Bryan Newman, PhD.
FDA/CDER/OGD/ORS/DTP
Sneha Dhapare, PhD.
FDA/CDER/OGD/ORS/DTP
Ross Walenga, PhD.
FDA/CDER/OGD/ORS/DQMM
Kairui Feng, PhD.
FDA/CDER/OGD/ORS/DQMM

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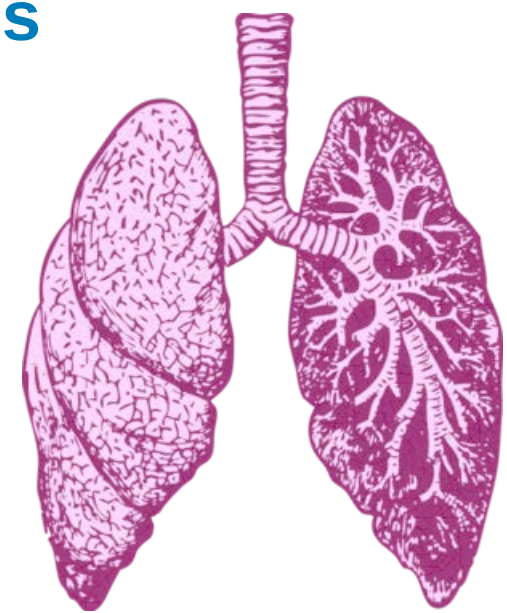
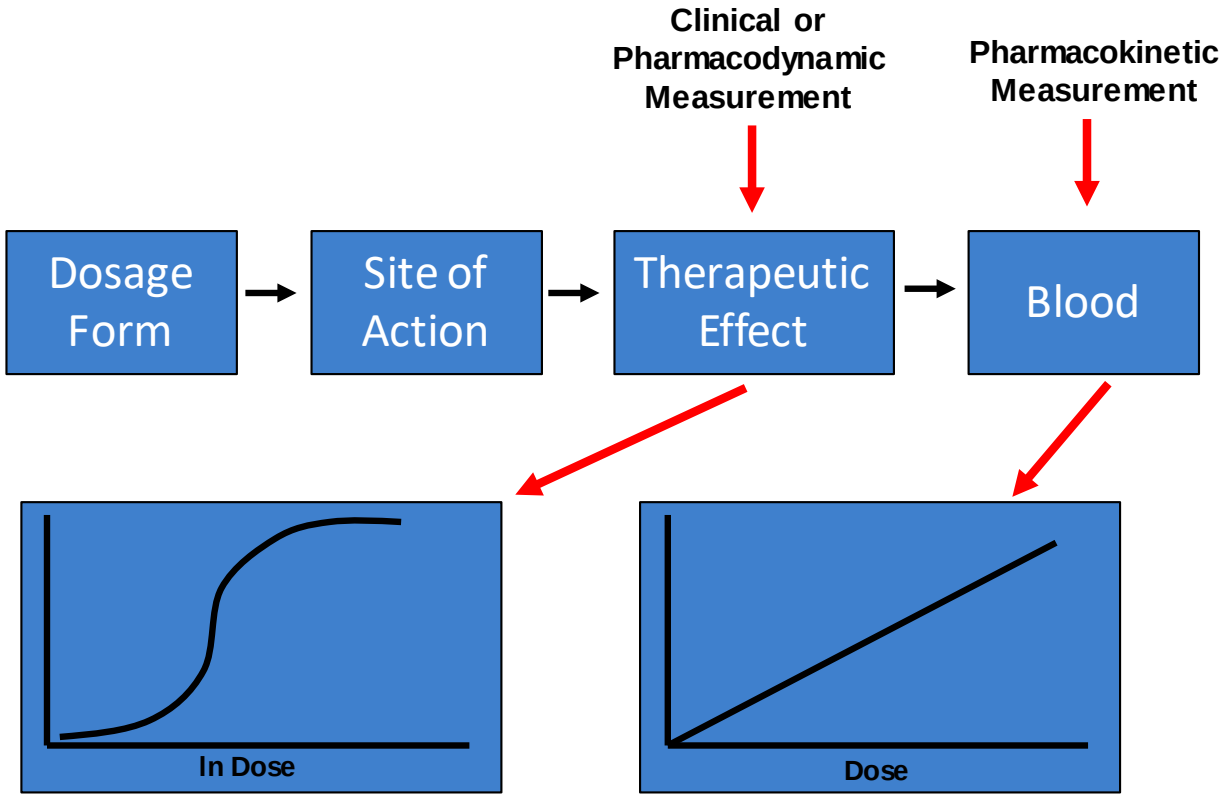


Patient-Related Challenges in Developing Locally Acting Generic OINDPs

- Respiratory tract disease
  - Asthma
  - Chronic obstructive pulmonary disease (COPD)
  - Rhinitis
- Regional distribution
- Site of action



Device-Related Challenges in Developing Locally Acting Generic OINDPs

- Drug-device combination products
- Designs vary significantly across dosage forms
- Patient-device interactions (e.g., user interface, patient's inhalation effort)

Orally Inhaled Products	Nasal Products

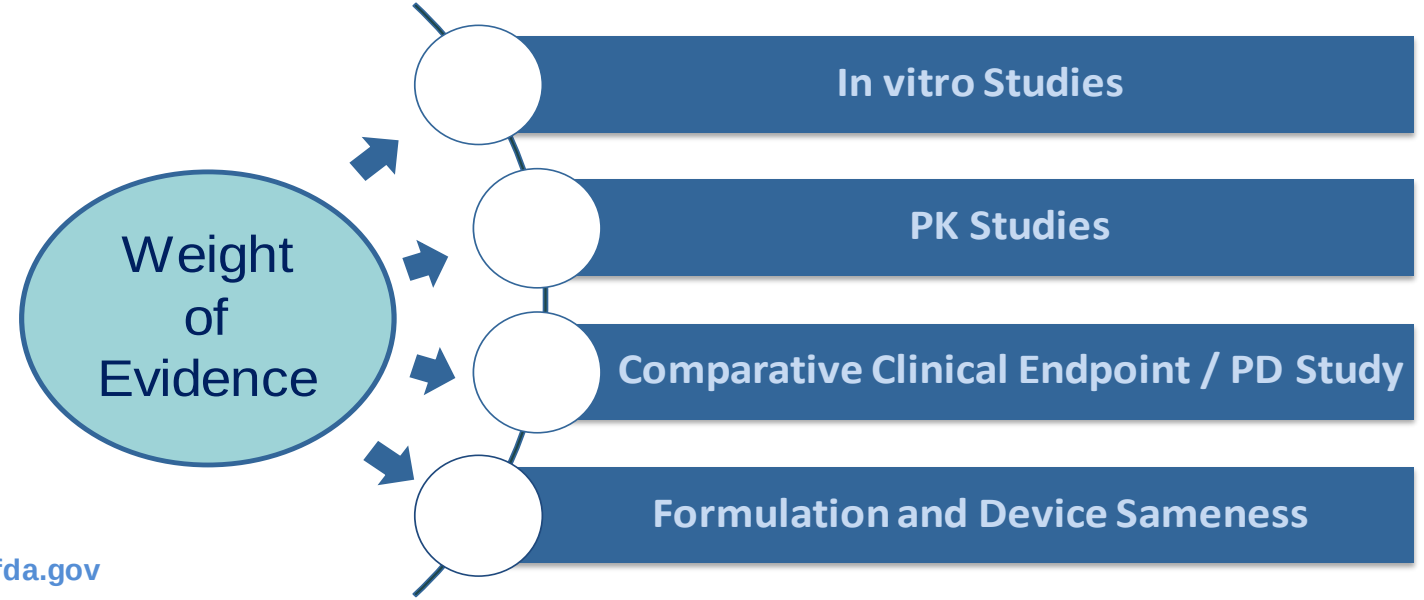
Formulation-Related Challenges in Developing Locally Acting Generic OINDPs

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

- Physicochemical properties
- Types and amounts of inactive ingredients

Establishing BE with OINDPs: Aggregate Weight-of-Evidence Approach

- Incomplete understanding of the relevance of results from BE studies to drug concentrations at local site of action in lung
- Uncertainties regarding sufficiency of correlation of in vitro to in vivo PK data to establish BE
- Product-specific guidances (PSGs) currently recommend this approach for locally acting dry powder inhaler (DPI), metered dose inhaler (MDI) and nasal suspension spray products



Recommended In Vitro BE Studies

- Sensitive for detecting differences between formulations (if present)
- Less variable and easier to control than comparative clinical endpoint BE studies
- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch
- SAC and APSD are critical attributes 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 (e.g., API/Carrier physicochemical properties, device properties, process conditions)
- For MDIs and nasal suspensions, priming / repriming studies are recommended if required by the R product (e.g., not recommended for breath-actuated MDIs)

DPIs	MDIs	Nasal Suspensions

- **Single Actuation Content (SAC)**
  - Beginning (B), middle (M) and end (E) lifestages
  - 3 flow rates
- **Aerodynamic Particle Size Distribution (APSD)**
  - B and E lifestages
  - 3 flow rates
	- **SAC**
	  - B, M and E lifestages
	- **APSD**
	  - B and E lifestages
	- **Spray Pattern**
	  - B lifestage
	  - 2 distances from actuator mouthpiece
	- **Plume Geometry**
	  - B lifestage
	- **Priming / Repriming**
	  - (if required by the R product)
		- **SAC**
		  - B and E lifestages
		- **Droplet Size Distribution by Laser Diffraction (LD)**
		  - B and E lifestages
		  - 2 distances from actuator orifice
		- **Drug in Small Particles/Droplets**
		  - B lifestage
		- **Spray Pattern**
		  - B lifestage
		  - 2 distances from actuator orifice
		- **Plume Geometry**
		  - B lifestage
		- **Priming / Repriming**
		  - (if required by the R product)

Recommended In Vivo Pharmacokinetic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Nasal Suspensions
Study Design	Fasting, single-dose, two-way crossover, comparative pharmacokinetic (PK) study		
Objective	Determine differences in systemic exposure between drug products		
Strengths	All strengths should be tested since the relationship between PK dose proportionality across multiple strengths, in vitro performance parameters, and product characteristics are not well understood		
Dose	A minimum number of inhalations sufficient for PK characterization using a sensitive analytical method		
Study Population	Healthy subjects		
BE Endpoints and Criteria	The 90% confidence interval for the geometric mean T/R ratios for AUC and Cmax should fall within the limits of 80 – 125%		

Recommended In Vivo Comparative Clinical Endpoint / Pharmacodynamic BE Studies

In Vivo BE Parameter	DPIs	MDIs	Nasal Suspensions
Study Design	• Randomized, placebo-controlled, parallel or crossover comparative clinical endpoint (CEP) or pharmacodynamic (PD) BE study • Comparative CEP should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Study sensitivity: Comparative CEP (effect over placebo), PD study (adequate dose-response)		• Randomized, placebo-controlled, parallel-group comparative CEP BE study • Comparative CEP should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Study sensitivity: Comparative CEP (effect over placebo)
Objective	Determine differences in local delivery at the site of action between drug products		
Strengths	Lowest labeled dose (comparative CEP study)		
Dose	Single or multiple-dose (based on mechanism of action)		Multiple-dose
Study Population	One patient population indicated in the approved labeling		
BE Endpoints and Criteria	The 90% confidence interval for the geometric mean T/R ratios for the endpoint(s) should fall within the limits of 80 – 125%		Change from the baseline mean reflective Total Nasal Symptom Score (rTNSS) to the treatment mean rTNSS, expressed in absolute units

Considerations for Comparative CEP BE Studies

- Comparative CEP BE studies less sensitive than other methods for BE
- Can be less controllable than in vitro BE studies since patient use of the drug product can vary (e.g., variable patient compliance or technique with dose administration)
- 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
- PSGs based on data from RLD programs

Other Considerations for In Vivo BE Studies with OINDPs

- Questions on whether the proposed BE clinical study protocol is acceptable
  - Comparative BE clinical study protocols are not pre-reviewed
    - Acceptability is determined during the scientific review of the ANDA
- To submit a request related to a comparative BE clinical protocol evaluation
  - For a specific question not covered by the PSG, submit a controlled correspondence requesting FDA to comment on the specific question
  - For evaluation of a comparative BE study design that deviates from that recommended in the PSG, submit a complex controlled correspondence (120 day) requesting FDA to evaluate the alternative approach
  - For questions that either encompass multiple review divisions, complex product development issues, or relate to an alternative BE approach for a complex product for which FDA has not issued a PSG, submit a pre-ANDA meeting package

FDA Draft Guidance "Controlled Correspondence Related to Generic Drug Development"
https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm583436.pdf
FDA Draft Guidance "Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA"
https://www.fda.gov/media/107626/download

Other Considerations for In Vivo BE Studies with OINDPs

- Questions on whether the T product is eligible for "biowaiver" of in vivo BE studies
  - FDA assessment process
    - In general, in vivo bioavailability (BA) or BE of complex OINDPs may not be self-evident, so that a request to simply "waive" in vivo BE studies based on 21 CFR 320.22 may not be granted
    - Product-specific
    - Case-by-case manner
    - Waiver request will be reviewed at time of submission
  - Information to submit to facilitate the assessment
    - Alternative BE approach
    - Rationale and justification for the proposal
    - Preliminary data, if available

Clinical Endpoints Recommended in PSGs for In Vivo BE Studies with OINDPs

Primary endpoint(s)	Study design	Treatment duration	Study subjects	API
FEV_1 AUC_{0-12} (first day) Trough FEV_1 (last day)	Parallel	4 weeks	Asthma patients	Fluticasone furoate; Vilanterol (DPI) Fluticasone Proprionate (DPI, MDI); Salmeterol Xinafoate (DPI, MDI)
	Parallel	6 weeks	Asthma patients	Budesonide; Formoterol fumarate dihydrate (MDI)
FEV_1 AUC_{0-12}	Parallel / Crossover[d)]	Single-dose	Asthma patients COPD patients Asthma patients	Salmeterol Xinafoate (DPI) Glycopyrrolate (DPI) Formoterol Fumarate (DPI)
FEV_1 AUC_{0-24}	Parallel / Crossover[d)]	Single-dose	COPD patients	Indacaterol Maleate (DPI) Tiotropium Bromide (DPI) Umeclidinium Bromide (DPI)
FEV_1 AUC_{0-6}	Parallel / Crossover[d)]	Single-dose	COPD patients	Aclidinium Bromide (DPI) Ipratropium Bromide (MDI)
Trough FEV_1 (last day)	Parallel	4 weeks	Asthma patients	Beclomethasone Dipropionate (MDI) Budesonide (DPI) Fluticasone Furoate (DPI) Fluticasone Propionate (DPI, MDI) Mometasone Furoate (DPI, MDI)
	Parallel	8 weeks	Asthma patients	Ciclesonide (MDI)
PC_{20}	Crossover	>4 visits, (wash-out ≥ 24 hours)	Stable mild asthma patients	Albuterol Sulfate (MDI) Levalbuterol (MDI)

Acronym:
MDI: Metered Dose Inhaler;
DPI: Dry Powder Inhaler;
FEV_1: Forced expiratory volume in one second;
AUC: including area under the serial FEV_1-time curve;
COPD: Chronic Obstructive Pulmonary Disease.

Dose-scale Modeling in Bioequivalence for In Vivo CEP BE Studies with OINDPs

- Current PSG recommendations
  - Bronchoprovocation study
  - Bronchodilatation study
- Application
  - PD response does not increase proportionally with dose
  - Comparative clinical endpoint study is lengthy and not ideal for BE determination
  - The BE of drug products is assessed by estimating relative bioavailability (F) on dose scale - not original scale of PD measurements
- Methodology
  - Repetitive sampling with replacement (bootstrap)
  - Fitting the E_{max} model to each "sample dose-response dataset"
  - Computing 90% CI (within 67-150%) for F Using Efron's bias corrected and accelerated (BCA) method

Mechanistic Modeling of OINDPs

- Mechanistic models include physiologically-based pharmacokinetic (PBPK) and computational fluid dynamics (CFD) models
- Especially useful if used throughout product development cycle
- Applications for generic OINDPs
  - Product development
  - Support alternative BE approaches

Mechanistic Model Examples

- CFD combined with PBPK to predict differences in local absorption according to formulation and device differences
  - Support alternative BE approach
  - May be combined with other in vitro tests
- CFD to inform lactose batch selection for DPIs
  - Reduce number of APSD experiments
- PBPK combined with virtual BE to predict outcome of PK study prior to study execution
  - Reduce likelihood of need to repeat PK study

Formulation Considerations

- Qualitative (Q1) sameness:
  - Same Inactive Ingredients
    - Critical to establishing equivalence between the test and reference DPI products
    - Choices can be limited, depending on the type of product (e.g., DPIs)
- Quantitative (Q2) sameness
  - Same inactive ingredient(s) but may differ in concentration (± 5%)
    - Should not exceed the levels used in other FDA-approved products with the same administration route without providing additional justification and qualifications for excipients
    - 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
- Information to submit to facilitate a controlled correspondence (CC) assessment
  - Up to 3 proposed T formulations per CC
  - Complete information about all excipients (e.g., complete names, grades, hydrate form)
  - Concentration (e.g., %w/w, %w/v) of excipients inside the container (e.g., canister, bottle, blister, capsule, reservoir)

OINDP Device Considerations

- Therapeutically equivalent products 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

OINDP Device Considerations

Hypothetical Reference MDI	Hypothetical Reference DPI
	
Hypothetical Test MDI	**Hypothetical Test DPI**
	

https://www.3m.com/3M/en_US/drug-delivery-systems-us/technologies/inhalation/mdi/

https://www.dreamstime.com/stock-photos-asthma-inhaler-image24790423

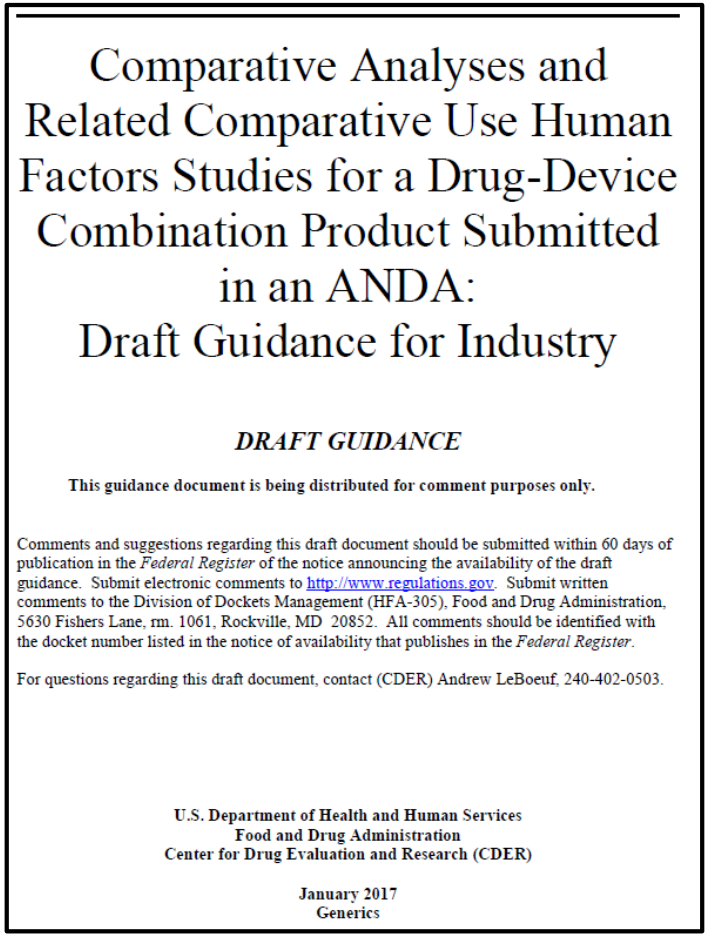
https://www.medgadget.com/2017/05/new-cheap-easy-manufacture-dry-powder-inhaler-developing-world.html

http://aedestra.com/blog/merxin-launches-mrx001-generic-blister-multidose-dry-powder-inhaler

- Examples of Device-related factors to consider
  - Presentation
    - e.g., Closed/Open
  - Energy Source
    - e.g., Active/Passive
  - Metering Principle
    - e.g., Blister/Capsule-Based/Single Use
  - Dose Number
  - Physical Appearance
    - e.g., Size/Shape/Color
  - Feedback Mechanism
    - e.g., Auditory/Tactile Sensations/Color Changes
  - External Critical Design Attributes
    - All device-related steps for delivering the drug
  - Cleaning Procedures
  - Dose Counter/Indicator

Choi, S., et al. Generic Drug Device Combination Products: Regulatory and Scientific Considerations. *Int J Pharm* 2018. June 15; 544(2): 443-454.

OINDP Device Considerations



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

https://www.fda.gov/media/102349/download

OINDP Device Considerations

- Comparative Analyses
  - Labeling Comparison
    - Side-by-side, line-by-line comparison: 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)]
  - Comparative Task Analysis
    - Assessed between T/R products
    - 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 R product physical features
    - Compare them to those of the proposed T delivery device constituent part for the combination product
    - Size, shape, visual or tactile feedback

OINDP Device Considerations

- 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 comparative 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
    - Potential Resolution:
      - Redesign user interface to minimize differences with R product
      - Potential need to additional information/data to support ANDA
      - Pre-ANDA Meeting Request or CC submission before conducting comparative use human factors studies

OINDP Device Considerations

- Information to submit to facilitate determining whether a T device may be acceptable for an ANDA submission
  - Samples of T and R devices
  - Comparative analyses
  - Specific question(s) based on the outcomes of the comparative analyses

Other Considerations for OINDPs

- General questions on "acceptability"
  - Examples of bad questions:
    - 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 communications
  - 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 the data has been reviewed
  - Requires involvement of multiple disciplines within the OGD
  - Requires involvement of other offices or centers within the Agency
- Ask specific, detailed questions about a complex situation or issue for your generic development program

Conclusions

- OINDPs are complex drug-device combination products
- The weight-of-evidence approach uses multiple determining factors to establish BE for locally-acting OINDPs
- This approach is detailed in OINDP PSGs that recommend the most accurate, sensitive, and reproducibile approach available for each prouct
- In addition to in vitro and in vivo performance, OINDP formulation properties (API / excipients), device components, and manufacturing process can affect performance, and so are considered in the evaluation of BE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Orally Inhaled and Nasal Drug Products (OINDPs): Quality Considerations

Dhaval Gaglani, MS
Branch Chief, Office of Lifecyle Drug Products
Office of Pharmaceutical Quality (OPQ), CDER / US FDA
2019 AAM GRx + Biosims Conference
November 6th, 2019

Orally Inhaled and Nasal Drug Products (OINDPs): Quality Considerations

- Complex drug products in that the container/closure system is integral to the delivery of the drug to the patient i.e., drug product performance
- The device delivers a specific amount of medication to the nasal cavity or the lungs
- Treatment:
  - Local (allergies, asthma, COPD, respiratory infections, and cystic fibrosis)
  - Systemic treatment (migraine, reversal of opioid overdose)

FDA Quality Guidance for Industry, OINDPs

- Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products-Quality Considerations

  https://www.fda.gov/downloads/drugs/guidances/ucm070573.pdf

- Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing and Controls Documentation

  https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf

USP Chapters

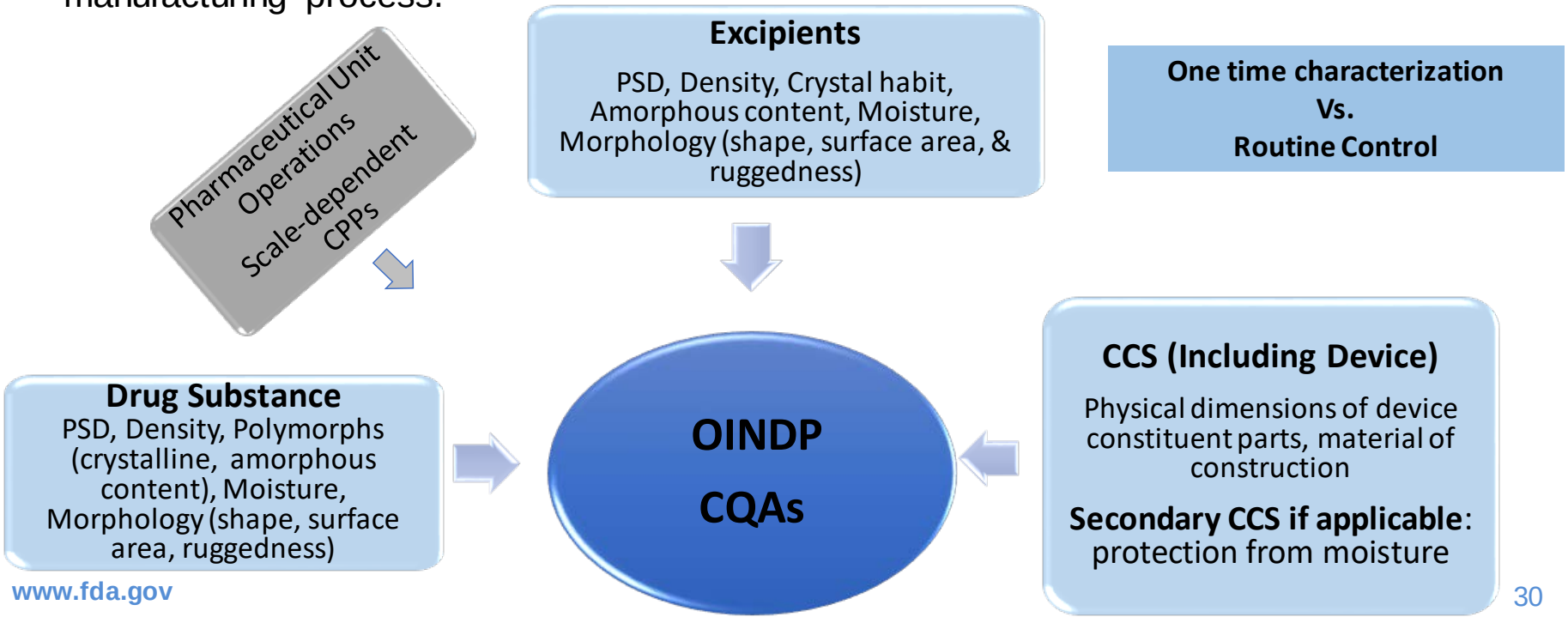
General Chapters:

- Chapter <5> Inhalation and nasal drug products-general information and product quality tests
  - Assessment of the integrity of the dosage form
- Chapter <601> INHALATION AND NASAL DRUG PRODUCTS: AEROSOLS, SPRAYS, AND POWDERS—PERFORMANCE QUALITY TESTS
  - Assessment of the delivery of the drug and other attributes that may relate to in vivo drug performance

Multiple Sources of Variability in OINDP Development

Upstream Variabilities collectively contribute to variabilities of product performance:

- Lot-to-lot variability of API(s), excipients and device constituent parts, CCS and manufacturing process.



Critical Quality Attributes (CQAs) for DPI, MDI and Nasal Suspension Products

DPIs	MDIs	Nasal Suspensions
- Assay - Degradation products - Delivered dose uniformity - APSD - Leachables - Moisture content - Net content - Particulate matter - Microbial limits	- Assay - Degradation products - Delivered dose uniformity - Valve delivery (shot weight) - APSD - Spray pattern - Leachables - Excipient/alcohol content - Moisture content - Net content - Particulate matter - Microbial limits	- Assay - Degradation products - Spray content uniformity - Droplet size distribution - Particle size distribution - Spray pattern and plume geometry - Leachables - Stabilizing excipient content - Net content - Particulate matter - Microbial limits - pH - Osmolality - Viscosity

Characterization Studies for DPI, MDI and Nasal Suspension Products

DPIs	MDIs	Nasal Suspensions
- In-use period - Temperature cycling - Effect of patient use - Effect of orientation of the device on delivered dose - Drug deposition on mouthpiece and/or accessories - Cleaning instructions - Profiling of actuations near device exhaustion - Effect of flow rate on DPI performance - Robustness	- In-use period - Temperature cycling - Effect of patient use - Priming and repriming - Drug deposition on mouthpiece and/or accessories - Cleaning instructions - Profiling of actuations near device exhaustion - Effect of flow rate and inhalation delay on MDIs with spacers - Robustness	- Priming and repriming in various orientations - Temperature cycling - In vitro dose proportionality (for multiple strength products) - Cleaning instructions - Device robustness - Effect of dosing orientation - Profiling of sprays near container exhaustion (Tail off characteristics) *Other characterization studies recommended in the guidance can be conducted as part of in vitro BE or routine control

Pre-ANDA Common Issues: Registration Stability (Exhibit) Batch Sizes and Packaging Strategy

- What is the acceptable batch size for registration stability batches?
  - One batch at the proposed commercial scale, the other two batches at 1/3rd commercial scale for MDI and DPI
- How many lots of drug substance, critical excipients and device components should be used to manufacture stability batches?
  - Three discrete batches of drug substances, critical excipients and device components are recommended
- Can single bulk lot of nasal spray split-filled to produce three registration stability batches?
  - Three discrete bulk lots are required to produce three registration stability batches for nasal sprays (suspension and solution)

Pre-ANDA Common Issues: Registration Stability (Exhibit) Batch Sizes and Packaging Strategy

- Is partial packaging of batches acceptable?
  - It is recommended to follow packaging requirements as per stability guidance
  - Alternate proposals may be sent for assessment in controlled correspondence

- Do registration stability batches need to be used in BE (in vitro/in vivo) studies?
  - It is recommended to use the registration stability batches to demonstrate in vitro BE
  - It is recommended to use at least one of these batches (i.e., biobatch) in a clinical study

Pre-ANDA Common Issues: Pre-Market Changes

- Which version of product should be used in registration stability and BE studies (in vitro and in vivo)?
  - "To be marketed" product (formulation, device, manufacturing process) should be used in registration stability and BE studies

- Do any studies (CMC and/or BE) need to be repeated if there is pre-market change in API source, formulation (e.g., change in PSD of carrier), device (e.g., design / supplier), manufacturing process (e.g., equipment, scale) or facility?
  - Product characterization and stability studies may need to be repeated
  - Bridging studies and justification for Quality and BE need to be provided
  - Pre-ANDA meeting is recommended

Pre-ANDA Issue: Device Quality System Regulation Information (according to 21 CFR Part 4)

- Questions related to design control or manufacturing control of the device constituent part of the combination product or the 21 CFR 820 requirements under part 4
  - Combination product are subject to CGMP requirements applicable to each constituent part (drug, device, biological product) of the combination product.
  - However, as reflected in final rule on CGMPs for combination products (21 CFR part 4), manufactures have options to demonstrate compliance both with drug CGMP regulations (21 CFR Parts 210, 211) and with the device quality system (QS) regulation (21 CFR Part 820) through a streamlined approach.
  - For further information on 21 CFR part 4, see *guidance for Industry and FDA Staff*: *Current Good Manufacturing Practice Requirements for Combination Products* (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

Other considerations at Pre-ANDA

- Ask specific, detailed questions about an issue for your generic drug development program!

Examples:

Specific questions:

- Considerations on establishment of APSD specification
- Study design/plan for the effect of patient use characterization study
- Stability studies at chosen orientation and justification

Avoid general/vague questions:

- Potential commercial device changes (limited information) and proposed in vitro comparative testing
- Proposed commercial release/shelf-life acceptance criteria based on development batches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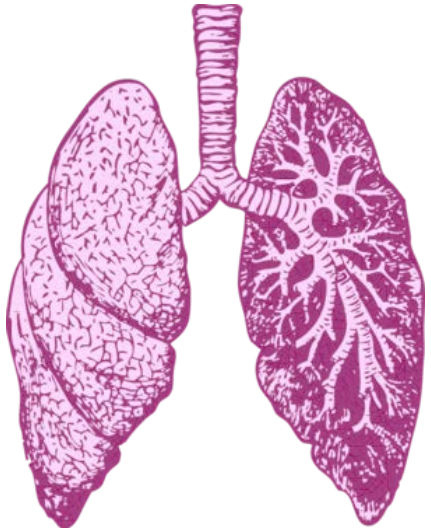
Hypothetical OINDP Breatheatol and the Pre-ANDA Meeting Request Process for OINDPs

Bryan Newman, PhD.
FDA/CDER/OGD/ORS/DTP
Sneha Dhapare, PhD.
FDA/CDER/OGD/ORS/DTP



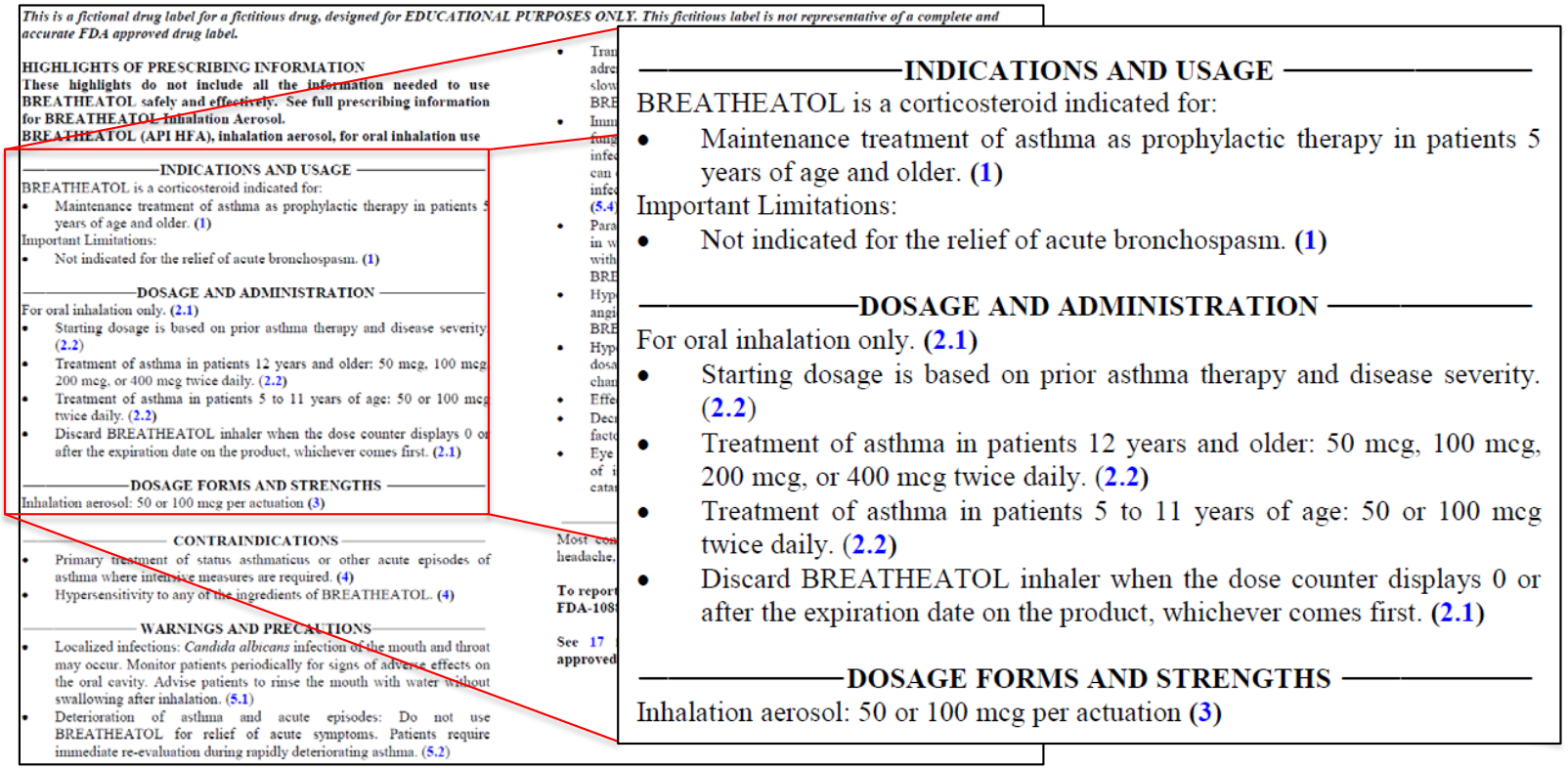
Pre-ANDA Meeting Requests

- Product Development meetings – designed to discuss specific scientific issues/questions, including novel proposed study designs, or alternative BE approaches
- FDA will provide targeted advice regarding an ongoing ANDA development program
- For details on Pre-ANDA meetings, refer to the FDA draft guidance for industry *Formal Meetings Between FDA and ANDA Applicants of Complex Products Under GDUFA*
- Meeting Request and Package:
  - Clear and specific questions about development program with a detailed rationale/justification and supportive data, which may include RLD and ANDA characterization, study design and pilot study results, comparison of the proposed approach to current BE recommendations, method validation/sensitivity, and quantitative analysis (PBPK, PK/PD, BE simulation) that supports the approach
  - If in silico approaches are proposed, rationale/justification on the different aspects of the modeling/simulation, including its development and verification, parameter selection and values, simulation design, literature sources, should be provided

Providing Background in Your Pre-ANDA Meeting Request: Labeling for Breatheatol

- The approved labeling for an RLD provides important information generic applicants should consider early in their generic drug development program
- Suppose your company is in the early stages of developing a generic to Breatheatol
  - What is some of the key information from Breatheatol's label that may be helpful for your development program?
  - Considering this information, how would you describe your proposed generic T product to the FDA?

Introduction to Hypothetical OINDP: Breatheatol



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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BREATHEATOL safely and effectively. See full prescribing information for BREATHEATOL Inhalation Aerosol.

BREATHEATOL (API HFA), inhalation aerosol, for oral inhalation use

INDICATIONS AND USAGE

BREATHEATOL is a corticosteroid indicated for:

- Maintenance treatment of asthma as prophylactic therapy in patients 5 years of age and older. (1)

Important Limitations:

- Not indicated for the relief of acute bronchospasm. (1)

DOSAGE AND ADMINISTRATION

For oral inhalation only. (2.1)

- Starting dosage is based on prior asthma therapy and disease severity (2.2)
- Treatment of asthma in patients 12 years and older: 50 mcg, 100 mcg, 200 mcg, or 400 mcg twice daily. (2.2)
- Treatment of asthma in patients 5 to 11 years of age: 50 or 100 mcg twice daily. (2.2)
- Discard BREATHEATOL inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. (2.1)

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: 50 or 100 mcg per actuation (3)

CONTRAINDICATIONS

- Primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required. (4)
- Hypersensitivity to any of the ingredients of BREATHEATOL. (4)

WARNINGS AND PRECAUTIONS

- Localized infections: *Candida albicans* infection of the mouth and throat may occur. Monitor patients periodically for signs of adverse effects on the oral cavity. Advise patients to rinse the mouth with water without swallowing after inhalation. (5.1)
- Deterioration of asthma and acute episodes: Do not use BREATHEATOL for relief of acute symptoms. Patients require immediate re-evaluation during rapidly deteriorating asthma. (5.2)

INDICATIONS AND USAGE

BREATHEATOL is a corticosteroid indicated for:

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Important Limitations:

- Not indicated for the relief of acute bronchospasm. **(1)**

DOSAGE AND ADMINISTRATION

For oral inhalation only. **(2.1)**

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- Treatment of asthma in patients 5 to 11 years of age: 50 or 100 mcg twice daily. **(2.2)**
- Discard BREATHEATOL inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first. **(2.1)**

DOSAGE FORMS AND STRENGTHS

Inhalation aerosol: 50 or 100 mcg per actuation **(3)**

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FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION

2.1 Administration Information

Administer BREATHEATOL by the orally inhaled route in patients 5 years of age and older. After inhalation, the patient should rinse his/her mouth with water without swallowing to help reduce the risk of oropharyngeal candidiasis. Patients should be instructed on the proper use of their inhaler. Consistent dose delivery is achieved, whether using the 50 or 100 mcg strengths, due to proportionality of the 2 products (i.e., 2 actuations of 50 mcg strength should provide a dose comparable to 1 actuation of the 100 mcg strength).

Priming: Patients should prime BREATHEATOL by actuating into the air three times before using for the first time or if BREATHEATOL has not been used for over 7 days. Avoid spraying in the eyes or face when priming BREATHEATOL.

Dose Counter: BREATHEATOL has a dose counter attached to the actuator. When the patient receives the inhaler, a black solid line will appear in the viewing window until it has been primed 3 times, at which point the total number of actuations will be displayed. The dose counter will count down each time a spray is released. The dose-counter window displays the number of sprays left in the inhaler in units of one (e.g., 120, 119, 118, etc). When the dose counter reaches 20, the color of the numbers will change to orange to remind the patient to contact their pharmacist for a refill of medication or consult their physician for a prescription refill. When the dose counter reaches 0, the background will change to solid red. Discard BREATHEATOL inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

2.2 Recommended Dosage

Adults and Adolescents 12 years of age and older: The starting dosage is based on previous asthma therapy and disease severity, including consideration of the patients' current control of asthma symptoms and risk of future exacerbation. The recommended starting dosage for patients 12 years of age and older who are not on an inhaled corticosteroid is 50 to 100 mcg twice daily, approximately 12 hours apart. For patients switching to BREATHEATOL from another inhaled corticosteroid product, select the appropriate starting dosage strength of BREATHEATOL based on the strength of the previous inhaled corticosteroid product and disease severity: 50, 100, 200 or 400 mcg twice daily. For patients who do not respond adequately to the initial dosage after 2 weeks of therapy, increasing the dosage may provide additional asthma control. The maximum recommended dosage for patients 12 years of age and older is 400 mcg twice daily.

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Pediatric Patients 5 to 11 years: The starting dosage is based on previous asthma therapy and disease severity, including consideration of the patient's current control of asthma symptoms and risk of future
approximately 12 hours apart. For patients w
BREATHEATOL 100 mcg twice daily may p
mcg twice daily.

11 DESCRIPTION

BREATHEATOL is a pressurized, metered-
propellant HFA-134a (1,1,1,2 tetrafluoroethan
from the actuator and 62.5 mcg from the val
products deliver 62.5 microliters (73.7 milli
canisters provide 120 inhalations each. BRE
when the inhaler has not been used for more t
chlorofluorocarbons (CFCs).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

API is a corticosteroid demonstrating pot
Corticosteroids have been shown to have
lymphocytes, macrophages, and neutrophils)
inflammatory actions of corticosteroids may

12.3 Pharmacokinetics

API undergoes rapid and extensive conversio
Absorption: The mean peak plasma concer
actuations of the 100 mcg/actuation strength
hour after inhalation of 400 mcg of BREA
mcg/actuation), equivalent systemic pharmac
Metabolism: Three major metabolites are fo
API rapidly to MET and more slowly to MET
Distribution: The *in vitro* protein binding fo
constant over the concentration range evaluat
Elimination: The major route of elimination
circulation. The mean elimination half-life
metabolites are mainly excreted in the feces.
Special Populations: Formal pharmacokinetic
Pediatrics: The pharmacokinetics of MET,
variable. In 20 children (mean age 12 years)
strength).

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11 DESCRIPTION

BREATHEATOL is a pressurized, metered-dose aerosol with a dose counter intended for oral inhalation only. Each unit contains a solution of API in propellant HFA-134a (1,1,1,2 tetrafluoroethane), sterile water, dehydrated alcohol, and anhydrous citric. BREATHEATOL 50 mcg delivers 50 mcg of API from the actuator and 62.5 mcg from the valve. BREATHEATOL 100 mcg delivers 100 mcg of API from the actuator and 125 mcg from the valve. Both products deliver 62.5 microliters (73.7 milligrams) of solution formulation from the valve with each actuation. The 50 mcg canisters and the 100 mcg canisters provide 120 inhalations each. BREATHEATOL should be "primed" or actuated three times prior to taking the first dose from a new canister, or when the inhaler has not been used for more than 7 days. Avoid spraying in the eyes or face while priming BREATHEATOL. This product does not contain chlorofluorocarbons (CFCs).

12.3 Pharmacokinetics

API undergoes rapid and extensive conversion to MET during absorption. The pharmacokinetics of MET has been studied in asthmatics given single doses.

Absorption: The mean peak plasma concentration (C_{max}) of API was 110 pg/ml at 0.625 hour after inhalation of 400 mcg using BREATHEATOL (4 actuations of the 100 mcg/actuation strength). The mean peak plasma concentration of the major and most active metabolite, MET, was 1774 pg/ml at 0.875 hour after inhalation of 400 mcg of BREATHEATOL. When the same nominal dose is provided by the two BREATHEATOL strengths (50 and 100 mcg/actuation), equivalent systemic pharmacokinetics can be expected. The C_{max} of MET increased dose proportionally in the dose range of 100 and 400 mcg.

Metabolism: Three major metabolites are formed via cytochrome P450-3A catalyzed biotransformation: MET, MET-2 and MET-3. Lung slices metabolize API rapidly to MET and more slowly to MET-2. MET is the most active metabolite.

Distribution: The *in vitro* protein binding for MET was reported to be 96-98% over the concentration range of 1250 to 6250 pg/mL. Protein binding was constant over the concentration range evaluated. There is no evidence of tissue storage of API or its metabolites.

Elimination: The major route of elimination of inhaled API appears to be via hydrolysis. More than 92% of inhaled API is found as MET in the systemic circulation. The mean elimination half-life of MET is 3.5 hours. Irrespective of the route of administration (injection, oral or inhalation), API and its metabolites are mainly excreted in the feces. Less than 12% of the drug and its metabolites are excreted in the urine.

Special Populations: Formal pharmacokinetic studies using BREATHEATOL were not conducted in any special populations.

Pediatrics: The pharmacokinetics of MET, including dose and strength proportionalities, is similar in children and adults, although the exposure is highly variable. In 20 children (mean age 12 years), the C_{max} of MET was 984 pg/ml at 0.75 hour after inhalation of 200 mcg (4 actuations of the 50 mcg/actuation strength).

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14 CLINICAL STUDIES

Blinded, randomized, parallel, placebo-controlled and active-controlled clinical studies were conducted in 1200 adult asthma patients to assess the efficacy and safety of BREATHEATOL in the treatment of asthma. Fixed doses ranging from 50 mcg to 200 mcg twice daily were compared to placebo. These studies provided information about appropriate dosing through a range of asthma severity. A blinded, randomized, parallel, placebo-controlled study was conducted in 450 pediatric patients (age 5 to 12 years) to assess the efficacy and safety of HFA API in the treatment of asthma. Fixed doses of 50 mcg and 100 mcg twice daily were compared with placebo in this study. In these adult and pediatric efficacy trials, at the doses studied, measures of pulmonary function [forced expiratory volume in 1 second (FEV_1) and morning peak expiratory flow (AM PEF)] and asthma symptoms were significantly improved with BREATHEATOL treatment when compared to placebo. In controlled clinical trials with adult patients not adequately controlled with beta-agonist alone, BREATHEATOL was effective at improving asthma control at doses as low as 50 mcg twice daily (100 mcg/day).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

BREATHEATOL is supplied in 2 strengths:

BREATHEATOL 50 mcg is supplied in a box of one 10.9 g canister containing 120 actuations with a plastic actuator with a dose counter and dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC AAAAA-AAA-AA.

BREATHEATOL 100 mcg is supplied in a box of one 10.9 g canister containing 120 actuations with a plastic actuator with a dose counter and dust cap, and Patient Information and Instructions for Use; box of one; 120 Actuations – NDC BBBBB-BBB-BB.

The correct amount of medication in each inhalation cannot be assured after 120 actuations from the 8.7 g canister even though the canister is not completely empty. Patients should be informed to discard the BREATHEATOL inhaler when the dose counter displays 0 or after the expiration date on the product, whichever comes first.

16.2 Storage and Handl

Store at 25°C (77°F). E

canister should be at roo

Aerosol actuator and the

so that the product rests

CONTENTS UNDER PRESSURE. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw container into fire or incinerator.

Keep out of reach of children.

Breatheatol Instructions for Use

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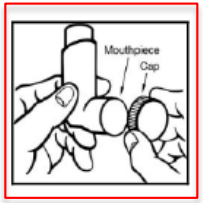
BREATHEATOL - PATIENT'S INSTRUCTIONS FOR USE

1. Remove the plastic cap and be sure there are no foreign objects in the mouthpiece.



2. Prime the inhaler before using for the very first time after purchase and when the inhaler has not been used for more than 7 days. Prime by releasing 3 sprays into the air, away from your eyes and face. Be sure the canister is firmly seated in the plastic mouthpiece adapter before each use.

3. Breathe out as fully as you comfortably can. Hold the inhaler as shown in figure below. Close your lips around the mouthpiece, keeping your tongue below it.

4. While breathing in deeply and slowly, press down on the can with your finger. When you have finished breathing in, hold your breath as long as you comfortably can (about 10 seconds).

5. Take your finger off the can and remove the inhaler from your mouth. Breathe out gently.

6. If your physician has told you to take more than one inhalation per treatment, repeat steps 3 through 5.

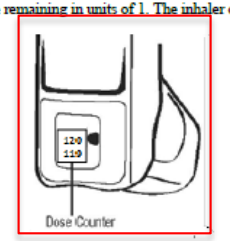
7. You should rinse your mouth with water after treatment.

8. For normal hygiene, the mouthpiece of your inhaler should be cleaned weekly with a clean, dry tissue or cloth. Do not wash or put any part of your inhaler in water.

9. Replace the cap over the mouthpiece after use.

INFORMATION ABOUT THE DOSE COUNTER

- The inhaler comes with a dose counter located on the back of the actuator (figure below). The dose counter window will show you the number of actuations (sprays) of medicine remaining in units of 1. The inhaler contains "120" actuations (sprays).



- The first time you use your inhaler, the dose counter will show "120" actuations remaining (figure above). Each time you press the canister, a spray of medicine is released and the dose counter will count down. When the dose counter reaches 0, it will continue to show 0 and you should replace your inhaler.
- Before priming, the inhaler will show a black solid line in the dose counter window (figure below). After priming 3 times, the dose counter should read "120."

- When the dose counter on the actuator shows the number 20, the color of the number will change to orange. The orange numbers are to remind you to refill your prescription or ask your doctor for another prescription for the inhaler. When the dose counter reaches 0, the background color will change to solid red.
- Throw the inhaler away as soon as the dose counter reads 0 or by the expiration date on the inhaler package, whichever comes first.

Formulation Considerations

- First steps for identifying the right formulation?
  - Reverse engineer the RLD
- How are OINDPs evaluated for Q1/Q2 assessment by FDA?
  - Q1 = same excipients; Q2 = ± 5% of excipient concentration in RLD
  - Compare RLD by concentration within the canister (typically as %w/w)
  - % difference = [(T – R) / R] x 100
  - Neither API concentration nor maximum daily dose (MDD) are part of Q1/Q2 assessment
- What information should be provided to the FDA for a Q1/Q2 assessment?
  - Up to 3 T formulations, one CC for each strength
  - Complete information about all excipients (e.g., complete names, grades, hydrate form, canister concentration)

RLD FORMULATION

INACTIVE INGREDIENT	Function	Weight per Canister (g)	Concentration (% w/w)
API	Active	0.00800	0.071
Citric Acid, USP (anhydrous)	Stabilizing Agent	0.00045	0.004
Purified Water, USP	Cosolvent	0.05610	0.500
Dehydrated Alcohol, USP	Cosolvent	1.68300	14.995
1,1,1,2-tetrafluoroethane (HFA-134a)	Propellant	9.47600	84.430
TOTAL		11.22355	100.000

Formulation Considerations

- Is the formulation below Q1/Q2 with the RLD?

Ingredients	RLD		Test Formulation		% Difference
	Weight per Canister (g)	Concentration % (w/w)	Weight per Canister (g)	Concentration % (w/w)	
API	0.00800	0.071	NA	NA	NA
Citric Acid, USP (Anhydrous)	0.00045	0.004	0.00043	0.004	0
Purified Water, USP	0.05610	0.500	0.05700	0.508	2
Dehydrated Alcohol, USP	1.68300	14.995	1.74000	15.508	3
1,1,1,2-tetrafluoroethane (HFA-134a)	9.47600	84.430	9.42257	83.980	-1

Formulation Considerations

- Is the formulation below Q1/Q2 with the RLD?

Ingredients	RLD		Test Formulation		% Difference
	Weight per Canister (g)	Concentration % (w/w)	Weight per Canister (g)	Concentration % (w/w)	
API	0.00800	0.071	NA	NA	NA
Citric Acid, USP (Anhydrous)	0.00045	0.004	0.00045	0.004	0
Purified Water, USP	0.05610	0.500	0.05610	0.500	0
Dehydrated Alcohol, USP	1.68300	14.995	1.90000	16.939	13
1,1,1,2-tetrafluoroethane (HFA-134a)	9.47600	84.430	9.26000	82.557	1

Constructing a Pre-ANDA Meeting Request: Formulation Options

Option 1:

Ingredients	RLD		Test Formulation		% Difference
	Weight per Canister (g)	Concentration % (w/w)	Weight per Canister (g)	Concentration % (w/w)	
API	0.00800	0.071	NA	NA	NA
Citric Acid, USP (Anhydrous)	0.00045	0.004	0.00043	0.004	0
Purified Water, USP	0.05610	0.500	0.05700	0.508	2
Dehydrated Alcohol, USP	1.68300	14.995	1.74000	15.508	3
1,1,1,2-tetrafluoroethane (HFA-134a)	9.47600	84.430	9.42257	83.980	-1

- Potential language to use in the Pre-ANDA meeting request?
  - T formulation deemed Q1/Q2 the same as per FDA's assessment in a previous controlled correspondence.
  - No formulation questions at this time.

Option 2

Ingredients	RLD		Test Formulation		% Difference
	Weight per Canister (g)	Concentration % (w/w)	Weight per Canister (g)	Concentration % (w/w)	
API	0.00800	0.071	NA	NA	NA
Citric Acid, USP (Anhydrous)	0.00045	0.004	0.00045	0.004	0
Purified Water, USP	0.05610	0.500	0.05610	0.500	0
Dehydrated Alcohol, USP	1.68300	14.995	1.90000	16.939	13
1,1,1,2-tetrafluoroethane (HFA-134a)	9.47600	84.430	9.26000	82.557	1

- Potential language to use in the Pre-ANDA meeting request?
  - Not applicable

Device Considerations

- What are the main differences between the test and RLD device?

RLD Device	Proposed Test Device
	

- Color
- Mouthpiece size/shape
- Cap size/shape
- Actuator size/shape

- How might these differences impact the user interface?

Device Considerations

- What are the main differences between the test and RLD device?

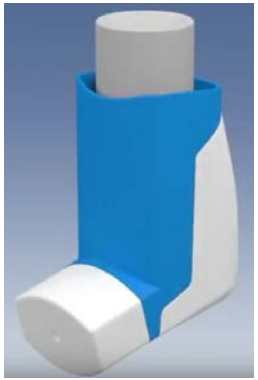
RLD Device	Proposed Test Device
	

  - Dose counter design and location

- How might these differences impact the user interface?

Device Considerations

- What are the main differences between the test and RLD device?

RLD Device	Proposed Test Device
	

- Overall larger size and shape
- No indication of a dose counter

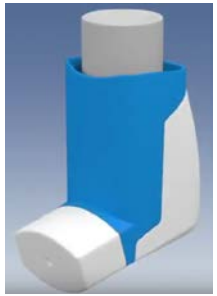
- How might these differences impact the user interface?

Device Considerations

- Best way to communicate with FDA for proposed T device user interface assessment?
  - Controlled Correspondence
- What should be submitted?
  - Samples of the to-be-marketed T and R devices
  - Comparative analyses results
  - Specific questions regarding identified differences in the user interface, along with justification
- If you determine a difference is "other than minor", what is your best course of action?
  - Applicants should consider submitting a pre-ANDA meeting request to discuss with the Agency how they plan on addressing these "other than minor" differences, and what types of additional data/information may be needed to support the T device's user interface substitutability with the R device

Constructing a Pre-ANDA Meeting Request: Device Options

Option 1:

RLD Device	Proposed Test Device 1
	

Note: T device is larger and no dose counter

- Potential language to use in the Pre-ANDA meeting request?
  - Size/shape differences identified as “other than minor”
  - Not expected to impact use based on literature sources
  - So these differences do not necessitate redesign or additional supportive information

Option 2

RLD Device	Proposed Test Device 2
	

Note: T device has dose counter differences

- Potential language to use in the Pre-ANDA meeting request?
  - Differences in dose counter location identified as minor
  - Not expected to impact use
  - No redesign or additional supportive data is needed

Considerations for In Vitro/In Vivo BE Studies

- If your conducted in vitro BE studies show performance differences (e.g., spray pattern), and require device modification to address this, what is the best scenario to move into your in vivo BE studies?

Next Steps: • Modify T Device • Repeat all in vitro BE studies • Demonstrate equivalent performance in 2 of 5 in vitro BE studies to R device • Move into in vivo BE studies	Next Steps: • Modify T Device • Repeat all in vitro BE studies • Demonstrate equivalent performance for all in vitro BE studies to R device • Move into in vivo BE studies
Important considerations: • If T device changes happen during the generic development program and the in vivo BE studies use a different T device version than the to-be-marketed device, bridging studies may be needed	• The best recommendation is to move to in vivo BE studies after the T product demonstrates equivalent performance to the R product in all in vitro BE studies

Considerations for In Vitro/In Vivo BE Studies

- Breatheatol is a solution MDI, so you don't believe in vivo BE studies are needed. What are your next steps and considerations for the following scenarios?

Plan: • Propose an alternative BE approach in lieu of the recommended in vivo BE studies, using a shorter study duration to improve recruitment/retention, and the highest strength	Plan: • Propose an alternative BE approach in lieu of the recommended in vivo BE studies, using more advanced in vitro studies (e.g., spray velocity characterization, APSD with more relevant mouth-throat models) in conjunction with modeling/simulation methods to better predict lung deposition
Method of Communication: • Pre-ANDA Meeting Request	Method of Communication: • Pre-ANDA Meeting Request
Important Considerations: • Since study duration is based on the RLD product characteristics • Comparative clinical endpoint BE studies are generally recommended to use the lowest strength for study sensitivity	Important Considerations: • May be feasible, provided sufficient rationale and justification is given, along with statistical plan for demonstrating BE using the alternative BE approach, and supportive preliminary data (if available)

Constructing a Pre-ANDA Meeting Request: Options for Performance Testing and BE

• Option 1: Preliminary in vitro studies show a difference in product performance related to the T device 1 internal design. • Current plan is to modify T device 1 and repeat the in vitro BE studies.	• Option 2: Since the product is a solution-based MDI, your company does not believe the recommended in vivo BE studies are necessary. • Current plan is to use an alternative BE approach using more advanced in vitro studies and modeling/simulation in lieu of conducting in vivo BE studies.

• Potential language to use in the Pre-ANDA meeting request?
  • Preliminary in vitro BE studies didn't demonstrate same performance as RLD
  • Source of performance difference linked to actuator internal dimensions
  • Propose to repeat all in vitro BE studies
  • Does FDA agree with this proposal?
	• Potential language to use in the Pre-ANDA meeting request?
	  • Working to select alternative BE approaches in lieu of conducting the comparative clinical endpoint BE study recommended in the PSG
	  • The selected methods will include more advanced in vitro studies (e.g., APSD using more relevant mouth-throat models) to predict drug lung deposition
	  • Meeting package includes details on the models currently marketed, what we proposed to purchase, and our rationale
	  • Does FDA agree with proposed model selected and should we use models from different companies?

Acknowledgements

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