PSG Recommendations and Updates for OINDPs

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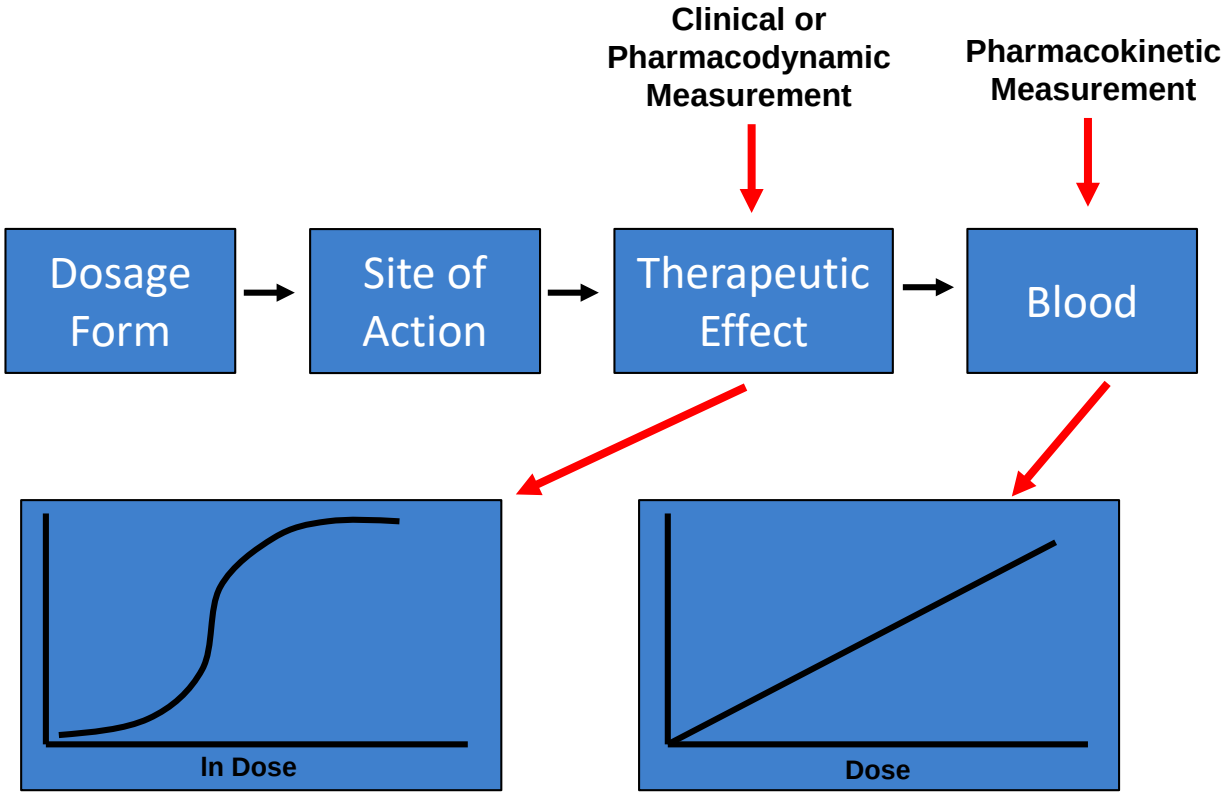
Outline

- Overview on orally inhaled and nasal drug products (OINDPs)
- Bioequivalence (BE) recommendations for OINDPs
- Recent updates to PSG recommendations

Patient-Related Challenges in Developing Locally Acting Generic OINDPs

- Respiratory tract disease
  - Asthma
  - 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

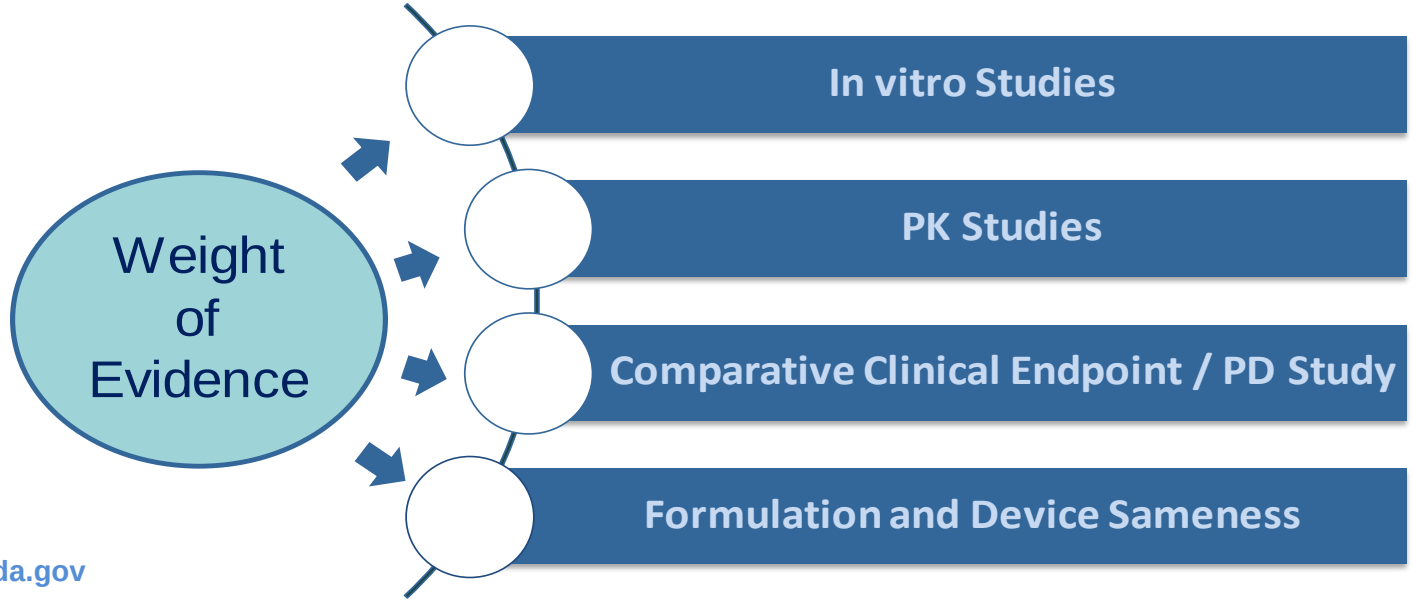
Formulation-Related Challenges in Developing Locally Acting Generic OINDPs

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



Currently Available OINDP PSGs

DPIs	MDIs	Nasal Solutions	Nasal Suspensions
1. Aclidinium bromide	1. Albuterol sulfate	1. Azelastine hydrochloride (2 PSGs)	1. Azelastine hydrochloride; Fluticasone propionate
2. Albuterol sulfate	2. Beclomethasone dipropionate (2 PSGs)	2. Beclomethasone dipropionate	2. Budesonide
3. Budesonide	3. Budesonide; Formoterol fumarate dihydrate	3. Calcitonin-salmon	3. Fluticasone furoate
4. Fluticasone furoate	4. Ciclesonide	4. Ciclesonide	4. Fluticasone propionate (2 PSGs)
5. Fluticasone furoate; Vilanterol trifenatate	5. Fluticasone propionate	5. Cyanocobalamin	5. Mometasone furoate monohydrate
6. Fluticasone propionate (2 PSGs)	6. Fluticasone propionate; Salmeterol xinafoate (2 PSGs)	6. Dihydroergotamine mesylate	6. Triamcinolone acetonide
7. Fluticasone propionate; Salmeterol xinafoate	7. Formoterol Fumarate; Mometasone furoate	7. Fentanyl citrate	
8. Formoterol fumarate	8. Ipratropium bromide	8. Ketorolac tromethamine	
9. Glycopyrrolate	9. Levalbuterol sulfate	9. Naloxone hydrochloride	
10. Indacaterol maleate	10. Mometasone furoate	10. Nicotine	
11. Mometasone furoate		11. Olopatadine hydrochloride	
12. Salmeterol xinafoate		12. Oxymetazoline hydrochloride; Tetracaine hydrochloride	
13. Tiotropium bromide		13. Sumatriptan	
14. Umeclidinium bromide		14. Zolmitriptan	

- **56%** of approved OINDPs have a PSG

Recommended In Vitro BE Studies

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)

- Conducted with all strengths, at least 3 batches of test (T) and reference (R) products, with no fewer than 10 units from each batch
- For MDIs and nasal suspensions, priming / repriming studies are recommended if required by the R product
  - Priming / repriming in vitro BE studies are generally not recommended for MDIs that are breath-actuated

Recommended In Vivo 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 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) study • Should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Comparison with placebo necessary to demonstrate study sensitivity		• Randomized, placebo-controlled, parallel-group comparative CEP study • Should contain a placebo run-in period followed by the treatment period of placebo, T, and R • Comparison with placebo necessary to demonstrate study sensitivity
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

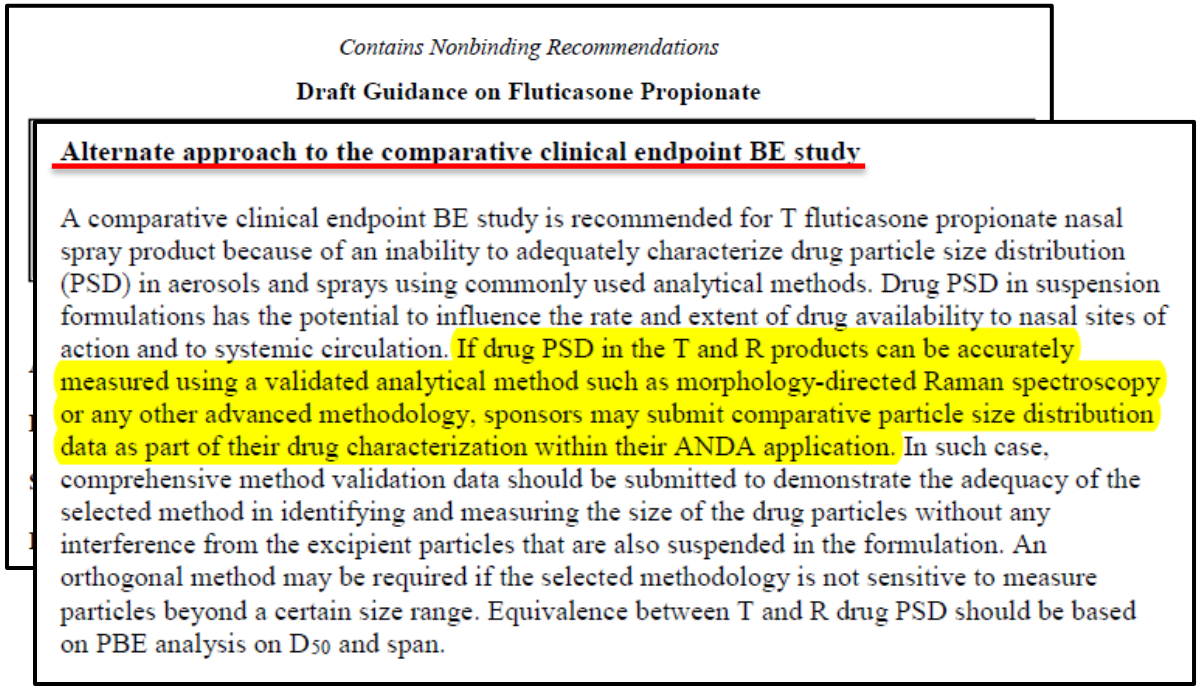
Recommended BE Approach for Nasal Solutions

Site of Action	Aqueous-Based Formulation	Non Aqueous-Based Formulation

Systemic Activity	- **Q1/Q2 Formulations**
	  - In Vitro Studies
	  - Type/design same as for nasal suspensions
	  - Potential for in vitro study waiver for drug in small particles/droplets and plume geometry for lower strength
	
	- **Non Q1/Q2 Formulations**
	  - In Vivo PK Study
	  - Design same as for nasal suspensions
	  - Conducted on the highest strength
	  - Potential for in vivo study waiver for lower strength
		- Not Applicable

Local Activity	- **Q1/Q2 Formulations**
	  - In Vitro Studies
	  - Type/design same as for nasal suspensions
		- **Q1/Q2 Formulations**
		  - In Vitro Studies
		  - Type/design same as for nasal suspensions
		  - Conducted with all strengths

PSG Recommendations for an Alternative BE Approach



Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate

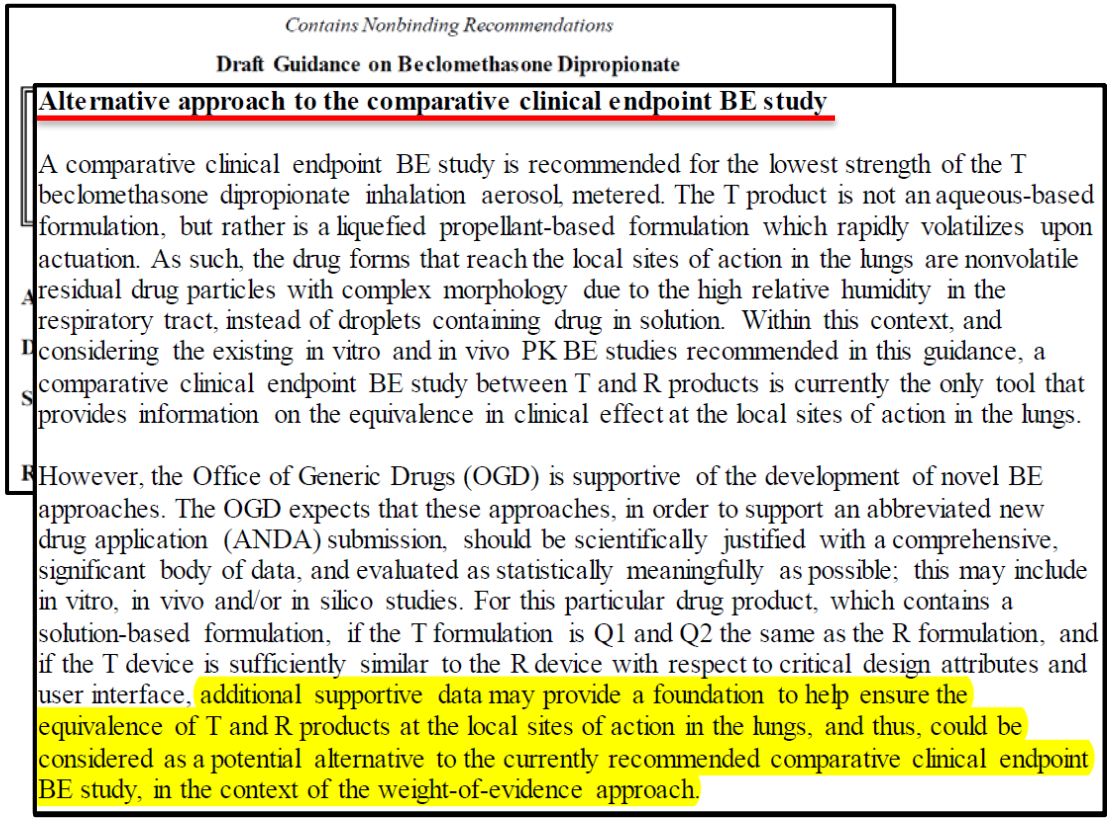
Alternate approach to the comparative clinical endpoint BE study

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

- Other nasal suspensions PSGs with alternative BE approach language:
  - Budesonide
  - Azelastine Hydrochloride and Fluticasone Propionate
  - Mometasone Furoate Monohydrate
  - Triamcinolone Acetonide

https://www.accessdata.fda.gov/drugsatfda_docs/psg/Fluticasone%20propionate%20nasal%20spray%20NDA%2002012 1%20RV%2002-2019.pdf

PSG Recommendations for an Alternative BE Approach



Contains Nonbinding Recommendations

Draft Guidance on Beclomethasone Dipropionate

Alternative approach to the comparative clinical endpoint BE study

A comparative clinical endpoint BE study is recommended for the lowest strength of the T beclomethasone dipropionate inhalation aerosol, metered. The T product is not an aqueous-based formulation, but rather is a liquefied propellant-based formulation which rapidly volatilizes upon actuation. As such, the drug forms that reach the local sites of action in the lungs are nonvolatile residual drug particles with complex morphology due to the high relative humidity in the respiratory tract, instead of droplets containing drug in solution. Within this context, and considering the existing in vitro and in vivo PK BE studies recommended in this guidance, a comparative clinical endpoint BE study between T and R products is currently the only tool that provides information on the equivalence in clinical effect at the local sites of action in the lungs.

However, the Office of Generic Drugs (OGD) is supportive of the development of novel BE approaches. The OGD expects that these approaches, in order to support an abbreviated new drug application (ANDA) submission, should be scientifically justified with a comprehensive, significant body of data, and evaluated as statistically meaningfully as possible; this may include in vitro, in vivo and/or in silico studies. For this particular drug product, which contains a solution-based formulation, if the T formulation is Q1 and Q2 the same as the R formulation, and if the T device is sufficiently similar to the R device with respect to critical design attributes and user interface, additional supportive data may provide a foundation to help ensure the equivalence of T and R products at the local sites of action in the lungs, and thus, could be considered as a potential alternative to the currently recommended comparative clinical endpoint BE study, in the context of the weight-of-evidence approach.

- Additional supportive data may include, but are not limited to:
  - More predictive APSD testing using representative mouth-throat models and breathing profiles
  - Characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates
  - Dissolution
  - Morphology imaging comparisons, including characterization of the full range of residual particle sizes
  - Quantitative method and modeling (for example, physiologically-based PK and computational fluid dynamic studies
  - Alternative in vivo PK BE studies
- ANDA applicants are strongly encouraged to discuss their development program for an alternative BE approach with FDA via the **Pre-ANDA Meeting Request** process
- Pre-ANDA Meeting Requests help to clarify the FDA's expectations for prospective applicants early in product development, and assist in submitting an ANDA as complete as possible

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

Conclusions

- OINDPs are complex drug-device combination products
- Product-Specific Guidances (PSGs)
  - Facilitate generic drug product availability
  - Assist generic pharmaceutical industry
  - Use the most accurate, sensitive, and reproducible approach available
  - Identify the current thinking methodology to support ANDA

Thanks

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