Nasal Products: Current Landscape and Recent Advancements

SBIA 2022: Advancing Generic Drug Development: Translating Science to Approval

Day 2, Session 6: Current Challenges and Scientific Advancements for Nasal Products

Bryan Newman, Ph.D.
Lead Pharmacologist
Division of Therapeutic Performance 1, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA
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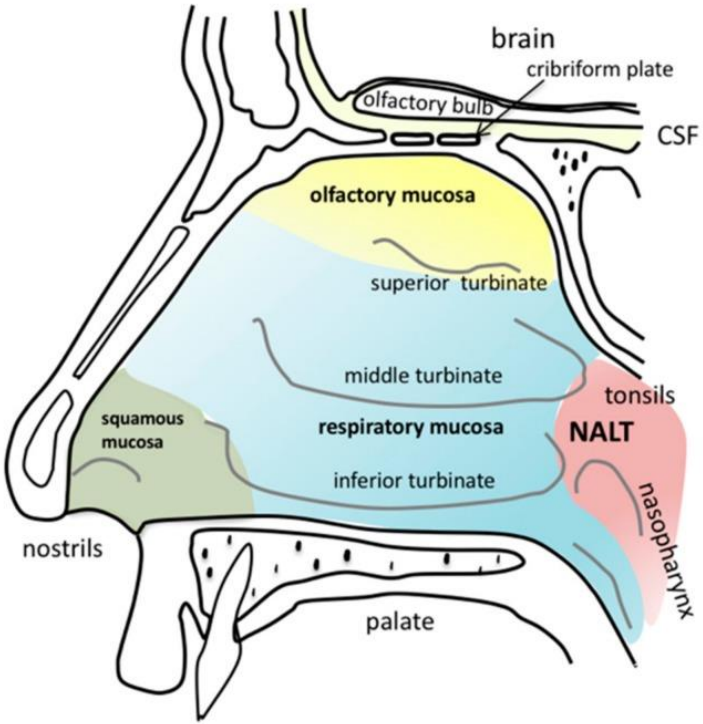
Learning Objectives

- Cover the fundamental concepts for drug delivery and establishing bioequivalence with nasal drug products
- Identify the alternative bioequivalence approaches that FDA has explored to address challenges with demonstrating equivalence with nasal suspensions through comparative clinical endpoint studies
- Describe the potential benefits in vitro nasal models and in silico methods can provide for evaluating nasal product performance
- Identify the bioequivalence approach recommended in the recently posted product-specific guidance for a nasal powder

Basics of Nasal Physiology

- Filters, warms and humifies incoming air[1,2,3]
- Total surface area (SA) = ~150 cm^2
- Can be divided into several regions
  - Nasal vestibule
    - Filtering; low SA; poor drug permeability
  - Atrium
    - Lower SA and vascularization
  - Respiratory region
    - Large SA; high vascularization; trigeminal nerves
  - Olfactory region
    - Lower SA but direct access to CNS
- Clearance mechanisms
  - Mucus production; 5 mm/min flow; renewed every 15-20 min
  - Ciliated epithelium; cilia beating facilitates mucus flow



https://upload.wikimedia.org/wikipedia/commons/b/b3/Anatomy_of_the_human_nasal_cavity.png

Nasal Diseases and Conditions

- Nasal diseases can present from a wide range of causes, including from other underlying medical conditions that affect more than one organ system[4,5]
- Rhinitis
  - Divided into three groups: infectious, allergic, and non-allergic
  - Infectious rhinitis
    - Can be bacterial, viral, fungal
    - Can be self-limiting
  - Allergic rhinitis
    - One of the most common medical conditions (9 – 42% in US)
    - Wide range of causes, including pollen, mold, dust, animal dander
  - Non-allergic rhinitis
    - Can be a chronic condition
    - Many sub-groups: drug-induced, hormone-induced, age-related, gustatory, occupational, atrophic, idiopathic
- Nasal polyposis
  - Masses up to 3 – 4 cm in diameter

Benefits for Nasal Drug Delivery

- Provides sites for local administration of treatments (e.g., corticosteroids, antihistamines, decongestants) for rhinitis and other conditions, which minimizes the doses and lowers potential for unwanted side effects[1,2]
- The nasal route of administration provides a potential alternative route for certain drugs typically given orally or by injection:
  - Generally noninvasive and painless
  - High vascularization provide opportunity for systemic drug delivery that can avoid first-pass metabolism
  - Beneficial for drugs with poor GI stability (e.g., peptides)
  - Potential for delivery directly to the CNS via olfactory region
  - Potential for vaccine delivery
- Drug delivery can still be challenging
  - Limited delivery volume
  - Clearance mechanisms

Methods for Nasal Drug Delivery

Nasal Sprays

- Typically pump-driven but propellant-driven and breath-aided products exists
- Aqueous and non-aqueous formulation within bottle/vial
- API can be suspended or in solution
- Deposits typically as formulation droplets

Nasal Aerosols

- Propellant-driven aerosolization
- Non-aqueous formulation in canister
- API in solution
- Deposits typically as dry particles or semi-dry particles upon evaporation of volatile components; may be dependent on formulation

Nasal Powders

- Patient breathe-driven aerosolization
- Powder within single-use nosepiece
- Solid blend of API particles/agglomerates with no excipients
- Deposits as dry particles of drug and/or agglomerates

Nasal Gels, Ointments, Solutions

- Pump or tube delivered; pledgets used for solution products
- Semisolid formulations can be paraffin/glycerin ester or castor oil/oleoyl polyoxylglycerides based
- API in solution or suspension
- Drug is directly applied to the nasal surface

Nasal Implants

- Physician applied using a hand-held delivery system
- Implant comprised of PLGA / PLCL with a coating of API embedded within a PLGA / PEG bioabsorbable polymer matrix
- Drug slowly released to the ethmoid sinus

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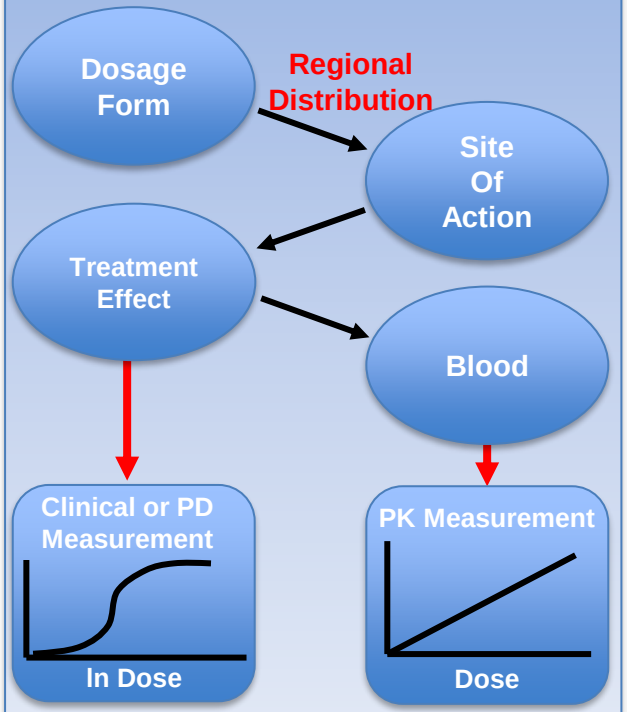
Sources of Complexity and Challenges with NDPs

Patient Related*

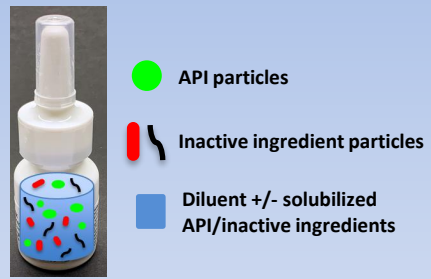


Device Related

- Drug-device combination products that vary significantly across dosage forms
- Patient-device interactions (e.g., user interface, insertion angle, actuation force)

Formulation Related

- API state
- Physicochemical properties
- Types and amounts of inactive ingredients



Route	Site of Action	API State	Dosage Form
Nasal	Local	Solution	Spray
		Solution	Solution
		Suspension	Ointment
		Solution	Aerosol, Metered
		Suspension	Spray
		Polymer-embedded	Implant
	Systemic	Solution	Gel
		Solution	Spray
		Suspension	Spray
		Solid Blend	Powder

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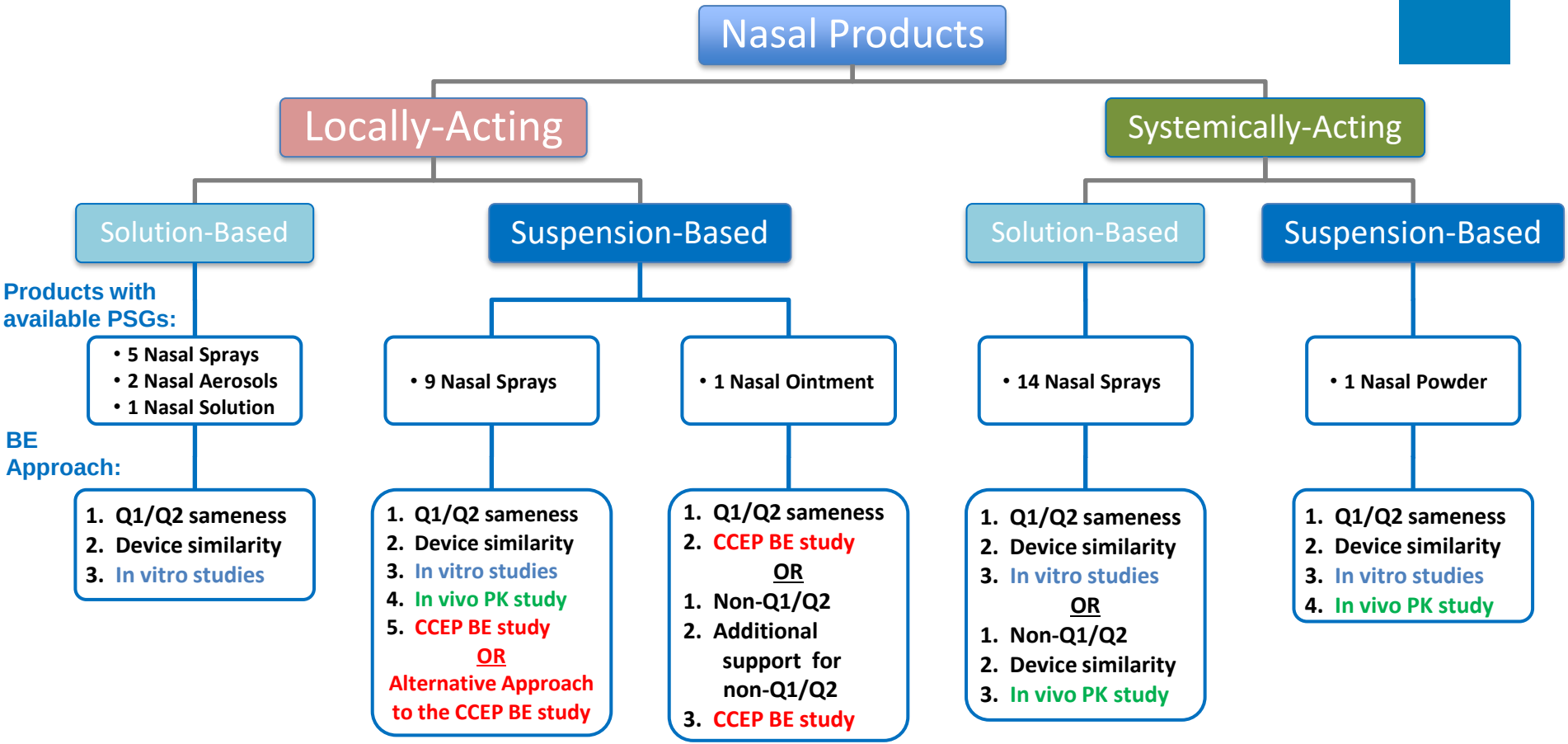
*For locally-acting products

PK: pharmacokinetic
PD: pharmacodynamic

API: Active pharmaceutical ingredient
NDP: nasal drug product

Current BE Recommendations for Nasal Products



PSG: Product-specific guidance
BE: Bioequivalence
CCEP: Comparative clinical endpoint

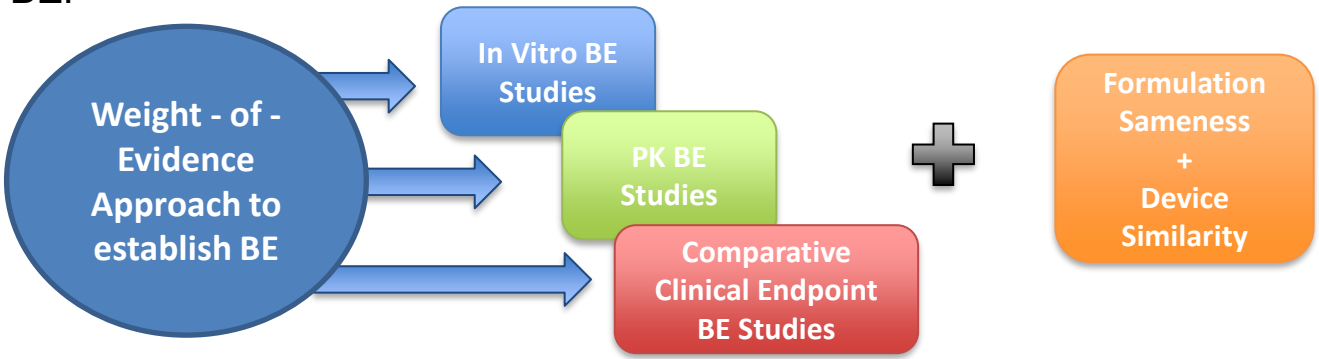
BE Considerations for Nasal Suspensions

- Drug particle size distribution (PSD) in nasal suspension formulations has the potential to influence **the rate and extent of drug availability** to nasal sites of action and systemic circulation.
- For nasal suspensions, drug particles are often formulated with a **suspending agent** along with other soluble inactive ingredients.
- Distinguishing drug particles from other suspended inactive ingredients can pose a significant analytical challenge.
- Nasal suspension PSGs recommend a weight of evidence approach for establishing BE.

Drug particles

Inactive ingredient particles

Diluent +/- solubilized drug/inactive ingredient



PSG: Product-specific guidance
PK: pharmacokinetic

Advancements in BE Assessment Strategies: Alternative Approaches for Nasal Suspensions

Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate

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

Active Ingredient:	Fluticasone propionate
Dosage Form; Route:	Metered, spray; Nasal
Strength:	0.05 mg/spray
Recommended Studies:	In vitro and in vivo studies

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.

- Nasal suspensions PSGs with alternative BE approach language:
  - Azelastine Hydrochloride and Fluticasone Propionate
  - Beclomethasone Dipropionate Monohydrate
  - Budesonide
  - Ciclesonide
  - Fluticasone Propionate
  - Mometasone Furoate Monohydrate
  - Triamcinolone Acetonide
- The Morphologically-Directed Raman Spectroscopy (MDRS) technique opens this possibility
  - Novel in vitro technology
  - Enables drug PSD comparison

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020121.pdf

FDA Communications for Technical Considerations

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ELSEVIER

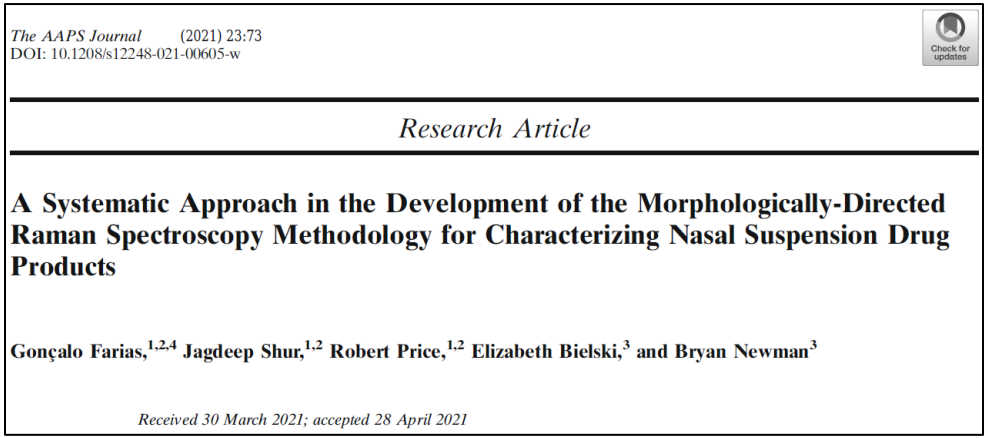
Pharmaceutics, Drug Delivery and Pharmaceutical Technology

Analytical method development for characterizing ingredient-specific particle size distributions of nasal spray suspension products

Check for updates

Brandon J. Thomas[a,1], Mohammad Absar[b,2], Renishkumar Delvadia[b,3], Denise S. Conti[b], Kimberly Witzmann[b,4], Changning Guo[a,*]

[a] Office of Testing and Research, Office of Pharmaceutical Quality, Food and Drug Administration, St. Louis, MO, United States
[b] Office of Research and Standards, Office of Generic Drugs, Food and Drug Administration, Silver Spring, MD, United States



The AAPS Journal (2021) 23:73
DOI: 10.1208/s12248-021-00605-w

Check for updates

Research Article

A Systematic Approach in the Development of the Morphologically-Directed Raman Spectroscopy Methodology for Characterizing Nasal Suspension Drug Products

Gonçalo Farias,[1,2,4] Jagdeep Shur,[1,2] Robert Price,[1,2] Elizabeth Bielski,[3] and Bryan Newman[3]

Received 30 March 2021; accepted 28 April 2021

- Recent articles have been published that provide details on experimental design and analysis of MDRS studies[6,7]
- The Agency's viewpoints for method development, validation, and BE considerations were also recently provided in a webinar hosted by AAPS in July 2022:[8]
  - *Scientific and Regulatory Considerations of Applying Morphology Directed Raman Spectroscopy in Bioequivalence Assessment for Generic Orally Inhaled Nasal Drug Products*

Are There Opportunities for Other Alternative Approaches?

- Nasal Suspension PSGs and FDA's guidance *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003)[9] emphasize the necessity for in vivo BE studies given the analytical challenges of distinguishing API particles from suspended inactive ingredients
- Morphology-directed Raman Spectroscopy is a capable alternative but also has its limitations
  - Challenges with characterizing particles at the lower particle size detection limits
  - Potential for difficulties from overlapping Raman signal
- Potential alternatives or supporting studies?
  - PK BE studies
  - Dissolution studies
  - In vitro studies using anatomical nasal models
  - In silico techniques

PSG: Product-specific guidance
API: Active pharmaceutical ingredient

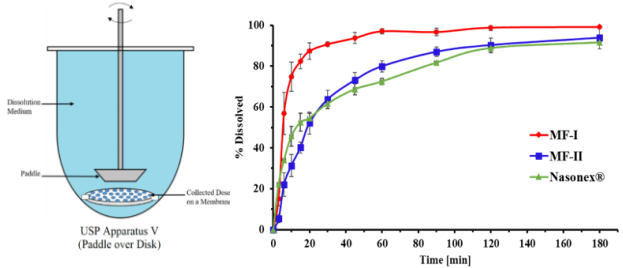
Assessing PK Sensitivity to PSD Differences

- Research contracts HHSF223201310220C (University of Florida) and 75F40120C00036 (Nanopharm)[10]
  - Evaluate whether PK studies could detect differences in nasal absorption between two nasal suspensions with different API PSDs
  - Compare PK sensitivity with other available in vitro methods (i.e., MDRS and dissolution studies)

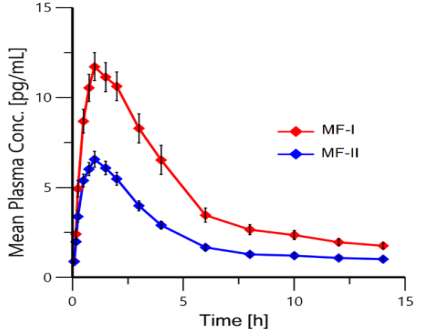
Nasal Formulation	Laser diffraction Bulk API Dv50 [µm]	Formulated suspensions		
		MDRS Dv10 (%CV) [µm]	MDRS Dv50 (%CV) [µm]	MDRS Dv90 (%CV) [µm]
MF-I	1.33	2.25 (2.51)	3.17 (4.34)	4.59 (4.99)
MF-II	3.43	2.56 (6.63)	5.50 (15.6)	10.6 (25.4)
Nasonex®	.	2.28 (6.14)	3.20 (28.8)	5.47 (23.4)

Note: MDRS data of MF-I and MF-II collected as part of contract 75F40120C00036; MDRS data of Nasonex® from Farias et al. 2021, AAPS J (collected as part of contract HHSF223201710163C)

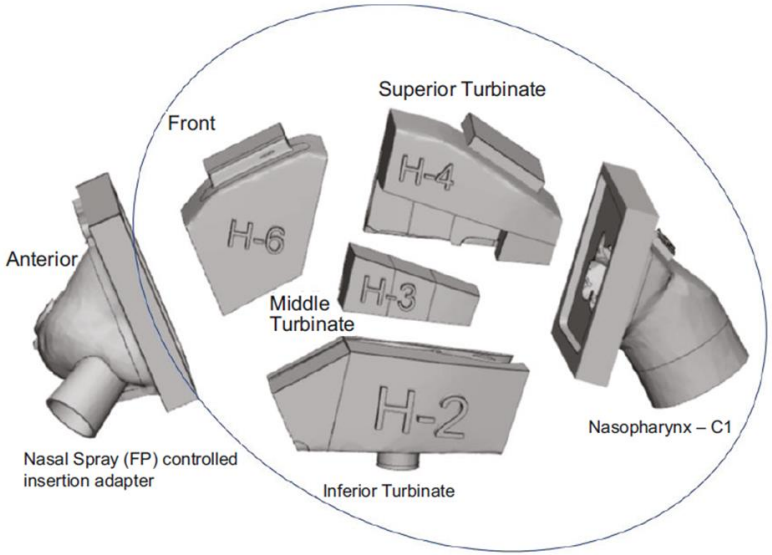
Dissolution



PK BE Study



What Can We Learn from Using Anatomical Nasal In Vitro Models?



Computational rendering of high posterior deposition model sectioned into anterior, front, inferior turbinate, middle turbinate, superior turbinate, and nasopharynx regions. (Fig. 4 of Golshahi et al.[11])

- For orally inhaled products, anatomical mouth-throat models have significant improved correlation with in vivo lung deposition data
  - Better estimation of mouth-throat deposition as compared to compendial methods
  - Evaluate inter-subject variability impacts
- Anatomical nasal models may offer a similar benefits for studying nasal products[11]
  - Better estimation of regional nasal deposition
  - Capacity to evaluate impacts of inter-subject variability in a range of patient populations (e.g., adult, pediatric)
  - Multiple research projects completed or ongoing

Advancements with In Silico Modeling of Nasal Product Performance

- Building a better understanding of how and why different product factors influence performance
  - Device design and patient use differences
  - Formulation differences
- Nasal deposition estimates from anatomical models may be useful for informing in silico models for comparing products or evaluating formulation impacts
- Multiple research projects completed or ongoing

	Fluticasone Furoate		Fluticasone Propionate	
	Anterior (%)	Posterior (%)	Anterior (%)	Posterior (%)
CFD quasi two-way coupling	93.4	6.6	89.5	10.5
CFD one-way coupling	92.6	7.4	94.0	6.0
In vitro	94.1 ± 1.9	5.9 ± 1.9	85.8 ± 5.4	14.2 ± 5.4
Relative error (quasi two-way coupling) (%)	0.7	11.9	4.3	26.1
Relative error (one-way coupling) (%)	1.6	25.4	9.6	57.7

Deposition predictions using two CFD methods with fluticasone furoate nasal spray and fluticasone propionate nasal spray as compared with in vitro data (n = 5).
(Based on Table 6 of Kolanjiyil et al.[12])

CFD: Computational Fluid Dynamics

Nasal Powder Product Complexity and BE Considerations

- Currently, only two products are marketed in the US
  - Onzetra® Xsail (sumatriptan succinate) nasal powder
    - Approved January 27, 2016
  - Baqsimi (glucagon) nasal powder
    - Approved July 24, 2019
- Can have unique device design and administration
  - Onzetra® Xsail uses a patient's breath to facilitate dose delivery
- Powder properties can influence nasal regional deposition and absorption
  - Multiple contributing factors for the API and inactive ingredient, including particle size, morphology, adhesion, density

https://www.onzetra.com/wp-content/uploads/2022/04/onzetra-application-device-for-migraine-relief.webp
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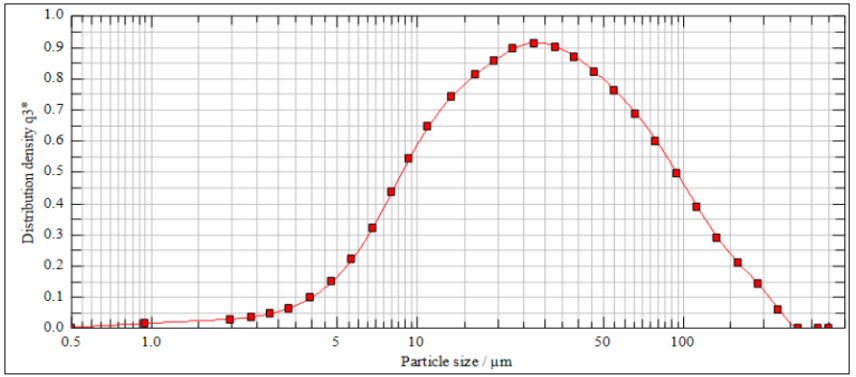
Nasal Powder Product Complexity and BE Considerations

- Considerations for BE recommendations for sumatriptan succinate nasal powder referencing Onzetra® Xsail
  - Formulation factors: no inactive ingredients, only API particles
  - Device factors: breath-powered administration
  - BE approach: in vitro alone or in combination with in vivo studies?
- OPQ/OTR assessed laser diffraction (LD) for utility as an in vitro BE study
- PSG recommendations posted March 2020[13]



PSD assessment of Onzetra® by Sympatec LD system equipped with a R4 lens

In Vitro Studies	In Vivo Studies	Additional Recommendations

• Single Actuation Content
  • B, M, E lifestages
  • 15, 30, 45 L/min using compressed air
  • 1 actuation; 2L volume
• Particle Size Distribution by LD
  • B, E lifestages
  • 30 and 45 L/min using compressed air
  • 1 distance b/w 2 – 7 cm from nosepiece tip
	• Fasting, single-dose crossover pharmacokinetic BE study
	  • EQ 11 mg Base strength
	  • EQ 22 mg Base sumatriptan (2 nosepieces, 1 per nostril)
	  • Adult males and non-pregnant, non-lactating females, general population
		• T formulation should contain same amount of drug substance in a powder form with no inactive ingredients
		• Device similarity

Challenge Question #1

Which of the following statements is NOT true?

A. Nasal administration is generally non-invasive and painless.

B. Nasal clearance mechanisms can pose challenges to drug delivery.

C. Nasal administration is not suitable for vaccine delivery.

Challenge Question #2

Anatomical nasal in vitro models may be beneficial for?

A. Better estimation of regional nasal deposition

B. Evaluating inter-subject variability in adult patients

C. Evaluating inter-subject variability in pediatric patients

D. All of the above

Conclusions

1. Nasal administration offers many opportunities for drug delivery, along with challenges for generic development and establishing BE.

2. To address these challenges, FDA continues to conduct research initiatives aimed at identifying alternative approaches with potential to support BE without the need for conducting comparative clinical endpoint BE studies.

3. Previous research has established that API particle size assessment using techniques like MDRS is an appropriate alternative BE approach to comparative clinical endpoint BE studies, which FDA has described in PSGs, publications and workshops.

4. Recent research efforts have also focused on understanding the capability of in vivo PK BE studies and dissolution studies for sensitively detecting API particle size differences for establishing BE.

5. Advances with anatomical nasal in vitro models and in silico modeling techniques have also provided new tools with potential for building a better understanding of nasal product performance.

6. As illustrate by the BE recommendations in the PSG for sumatriptan succinate nasal powder, nasal powders can present unique usage and performance attributes that should be considered when evaluating BE.

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Questions?

Bryan Newman, PhD
Lead Pharmacologist
Division of Therapeutic Performance 1, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA

Bryan.Newman@fda.hhs.gov


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