Alternative BE Approaches and Considerations for Nasal Products

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

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

Susan Boc
Scientific Researcher
Division of Therapeutic Performance-1, Office of Research and Standards, Office of Generic Drugs
CDER | U.S. FDA
September 21, 2022

Learning Objectives

- Describe the approach to establish bioequivalence (BE) for nasal products
- Explain the rationale behind recommendations for the pharmacokinetic (PK) BE study and the Comparative Clinical Endpoint (CCEP) BE study for nasal suspension products
- Describe the recommended alternative approach to the CCEP BE study
- List the considerations from ORS research findings relevant to the alternative approach to the CCEP BE study

Weight-of-Evidence Approach for Nasal Suspensions

Weight-of-Evidence Approach to Establish BE

Equivalent In Vitro Performance demonstrated through comparative in vitro studies*

- Should lead to comparable deposition location and patterns at the site of action to ensure similar absorption from the nasal passages and regions of the airways beyond the nose into the systemic circulation

However, in vitro studies have limitations:

- In vitro in vivo correlations have not been clearly established
- Drug particle size distribution (PSD) has the potential to influence the rate and extent of drug availability to nasal sites of action and to the systemic circulation,[1] but difficult to identify due to interference of suspended excipients (e.g., cellulose)[2]

Therefore, BE recommendations currently include in vivo studies

Equivalent Systemic Exposure demonstrated through a comparative PK study

- To ensure comparable systemic adverse events; provides indirect evidence to support equivalence in local delivery

Equivalent Local Delivery demonstrated through a comparative clinical endpoint study

- To confirm the lack of important clinical differences between test and reference listed drug (RLD) products to provide evidence to assure equivalent local drug delivery

* Single Actuation Content, Droplet Size Distribution, Drug in Small Particles/Droplets, Spray Pattern, Plume Geometry, Priming and Repriming

[1] FDA Draft guidance for industry, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003)

[2] Vo A, et al. *Int J Pharm.* 2021; 598:120401.

Addressing the Challenges from the CCEP BE Study

Alternative BE Approaches

CCEP BE Study Challenges:

- **Higher Variability and Lower Sensitivity than Other BE Methods**
- **Time and Cost**

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, prospective applicants 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.

- *Fluticasone Propionate Nasal Spray, Metered* (June 2020)
- *Fluticasone Furoate Nasal Spray, Metered* (June 2020)
- *Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered* (June 2020)
- *Mometasone Furoate Nasal Spray, Metered* (June 2020)
- *Triamcinolone Acetonide Nasal Spray, Metered* (June 2020)
- *Budesonide Nasal Spray, Metered* (Aug 2020)
- *Ciclesonide Nasal Spray, Metered* (November 2021)
- *Beclomethasone Dipropionate Monohydrate Nasal Spray, Metered* (November 2021)

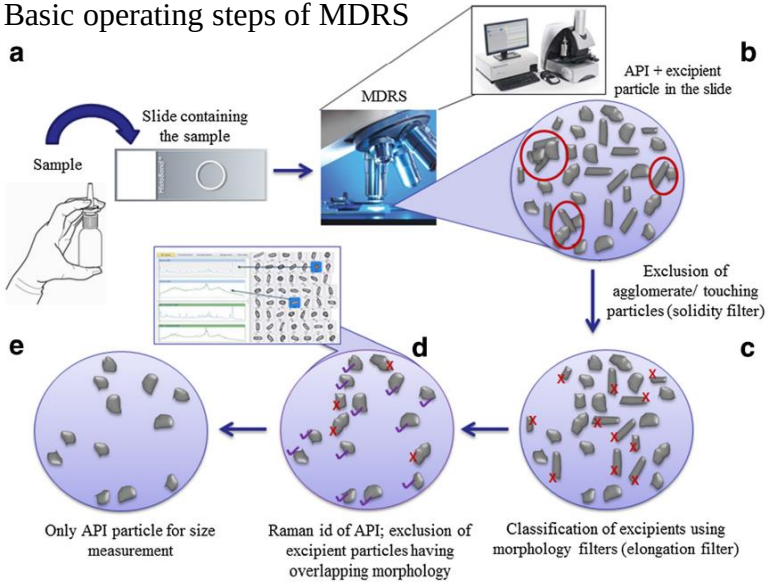
https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_020121.pdf

Alternative Approach to the CCEP BE Study

- In March 2016, FDA approved first generic Mometasone Furoate (MF) Nasal Suspension Spray based on weight-of-evidence approach and supportive data generated by Morphologically-Directed Raman Spectroscopy (MDRS)
- MDRS is an integrated method that measures particle morphological characteristics (size and shape) using its microscopic component, and performs chemical identification by analyzing Raman spectra
  - May be utilized for ingredient-specific PSD measurement
  - For products with only drug suspended as particles, other techniques (e.g., laser diffraction) may be sufficient for PSD measurement
  - Limitation: inability to measure particles <1 µm; may require use of orthogonal methods to assess submicron API particles

➢ In October 2016, this alternative approach to the CCEP BE study was provided in the product-specific guidance (PSG) on *Triamcinolone Acetonide Nasal Spray, Metered*

Basic operating steps of MDRS



a Sample preparation; **b** morphological measurement of particles, exclusion of aggregates and touching particles; **c** use of morphology filters to select particle of interest; **d** identification of particles using Raman spectra; **e** size measurement of particle of interest

API = Active Pharmaceutical Ingredient

Liu Q, et al. *AAPS J.* 2019; 21(2):14.

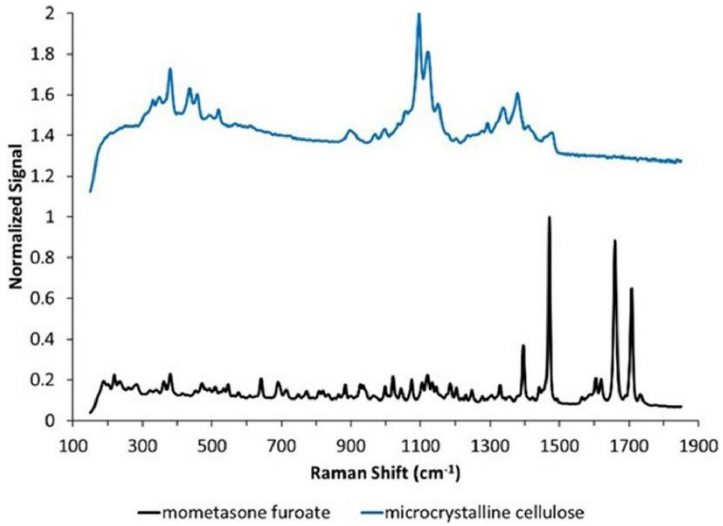
ORS Research on API Particle Size in Nasal Suspension Products

API PSD Characterization Using MDRS

Internal collaboration with the Office of Testing and Research in the Office of Pharmaceutical Quality

Objective: To develop a robust and reliable MDRS method for characterizing API particles in nasal spray suspension products.

- Nasonex® was used as the model nasal spray suspension; MF and microcrystalline cellulose (MCC) are suspended in the aqueous-based formulation
- Method development procedure included 5 steps:
  1. Sample preparation
  2. Particle imaging and morphology analysis
  3. Particle Raman measurements and classification
  4. Morphology filter selection
  5. Determination of minimum number of particles
- Raman measurements of the chemical standards of MF and MCC were performed to create spectra library for the two chemical species

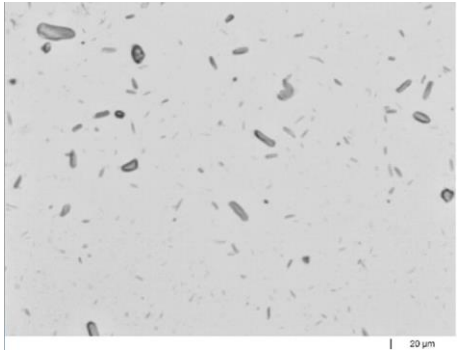


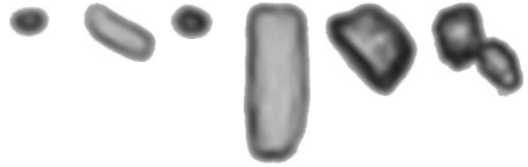
Thomas BJ, et al. *J Pharm Sci*. 2021; 110(7):2778.

API PSD Characterization Using MDRS

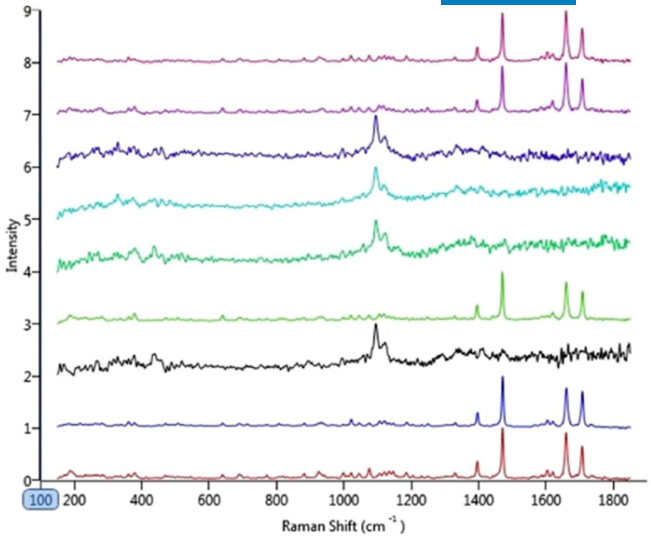
Results:

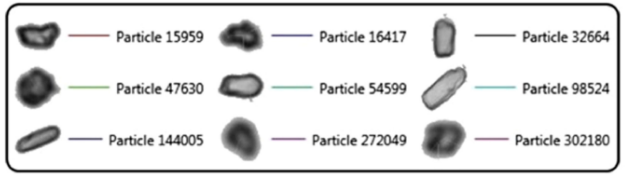
1. Optimized sample preparation: 5 µL sample wet dispersion with a circular-shape quartz coverslip
2. Particle imaging and morphology analysis: morphology analysis of over 10,000 particles found two distinct groups of particles
3. Particle Raman measurements and classification: Comparison of Raman spectra from 10,000 particles to the Raman spectra library resulted in correlation values > 0.9 for all API particles





Particle #	1	2	3	4	5	6
CE Diameter	2.28 µm	4.69 µm	2.53 µm	8.91 µm	7.36 µm	6.85 µm
Aspect Ratio	0.740	0.460	0.822	0.418	0.709	0.585
Circularity	0.965	0.860	0.974	0.853	0.937	0.795





Correlations

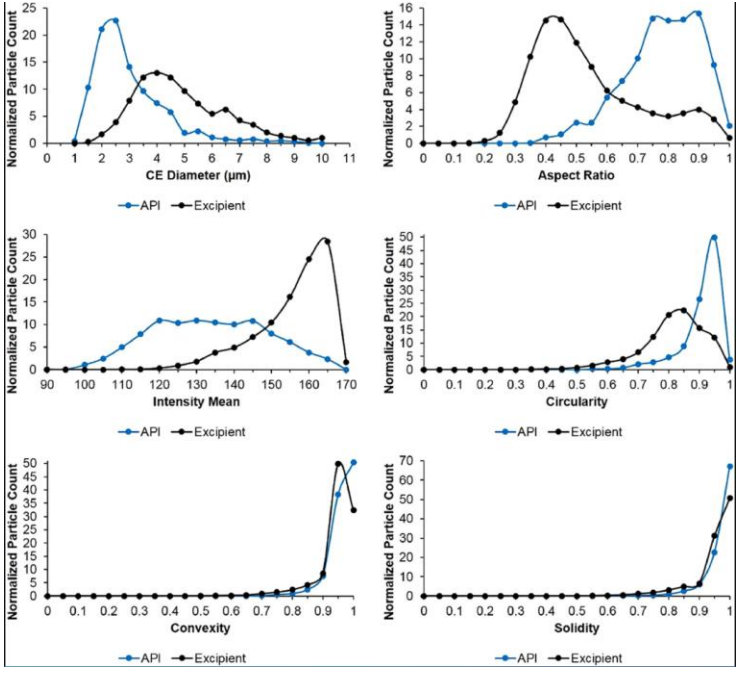
	Particle ID 15959	16417	32664	47630	54599	98524	144005	272049	302180
API	0.975	0.980	0.086	0.983	0.052	0.000	0.001	0.976	0.981
excipient	0.000	0.000	0.709	0.000	0.697	0.689	0.707	0.000	0.000

Thomas BJ, et al. *J Pharm Sci*. 2021; 110(7):2778.

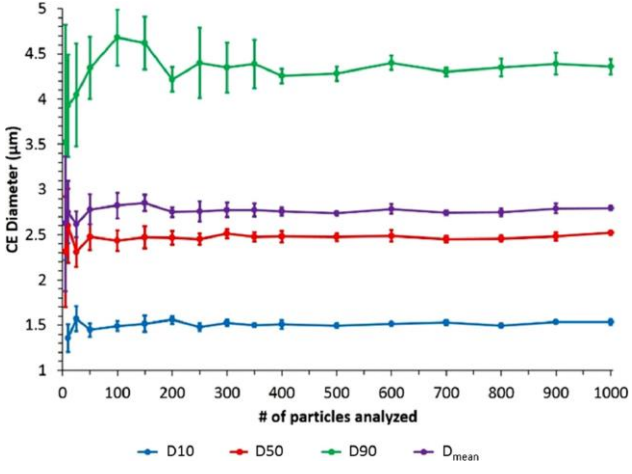
API PSD Characterization Using MDRS

Results (cont.):

4. Morphology filter selection: morphology distribution curves of the particles showed aspect ratio and intensity mean as the two most efficient parameters to separate API and excipient particles



5. Number of minimum particles: Accuracy (mean value) and repeatability (%RSD) of API PSD measurements were consistent when particle count was 400 and above



Product-specific experimental parameters were determined for MF nasal suspension

Thomas BJ, et al. *J Pharm Sci*. 2021; 110(7):2778.

Alternative Approaches for Detecting API PSD Differences

Contract HHSF223201310220C with University of Florida and contract 75F40120C00036 with Nanopharm

Objective: Evaluate whether selected in vitro and PK studies would be able to differentiate between suspension-based nasal spray formulations that differ in API PSD

- MF nasal suspensions were manufactured to be qualitatively and quantitatively the same as Nasonex® but have different Dv50 values

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)

➢ MDRS revealed the formulation MF-I was shown to have API particle size comparable to Nasonex®

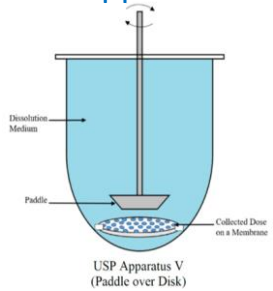
Hochhaus G, et al. *RDD 2022.* Volume 1: 47-54.

Alternative Approaches: Impact of MF PSD on In Vitro Data

Dissolution tests were performed with USP Apparatus V and Transwell® systems

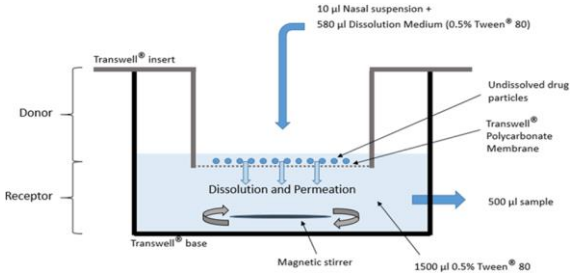
- Dissolution media: 0.5% Tween 80 in distilled water at 37°C

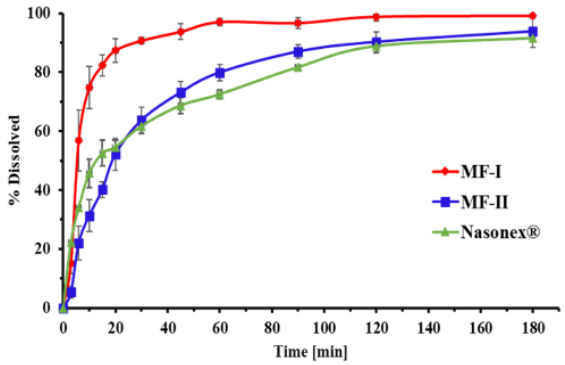
USP Apparatus V

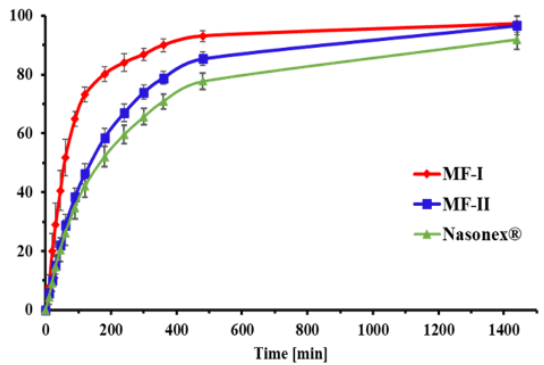


USP Apparatus V
(Paddle over Disk)

Transwell®







	Dv50 Laser [µm]	Dv50 (%CV) [µm]	VMD (GSD) [µm] USP Apparatus V	VMD (GSD) [µm] Transwell®
MF-I	1.33	3.17 (4.34%)	5.55 (1.44)	9.05 (2.12)
MF-II	3.4	5.50 (15.58%)	10.42 (1.76)	20.84 (1.82)
Nasonex®		3.20* (28.75%)	9.12 (2.56)	23.68 (2.08)

* Farias et al. 2021, AAPS J

For both systems:

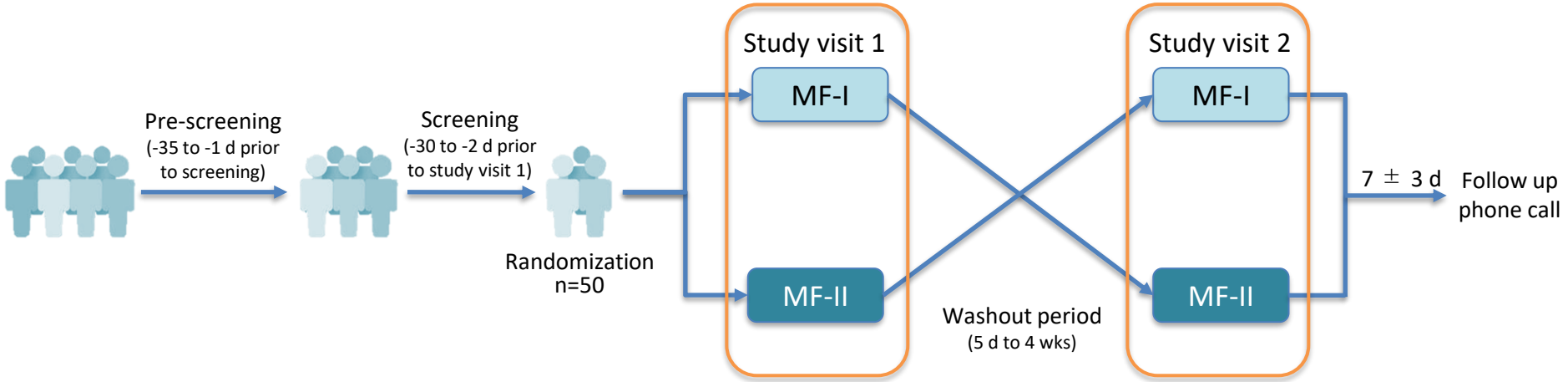
- **Dissolution tests were able to differentiate formulations with different API particle size**
- Dissolution of MF-II was comparable to Nasonex®

Hochhaus G, et al. *RDD 2022.* Volume 1: 47-54.

Alternative Approaches: Impact of MF PSD on In Vivo Data

A PK study was performed with the two manufactured batches

- Two-way, double-blind crossover with charcoal block

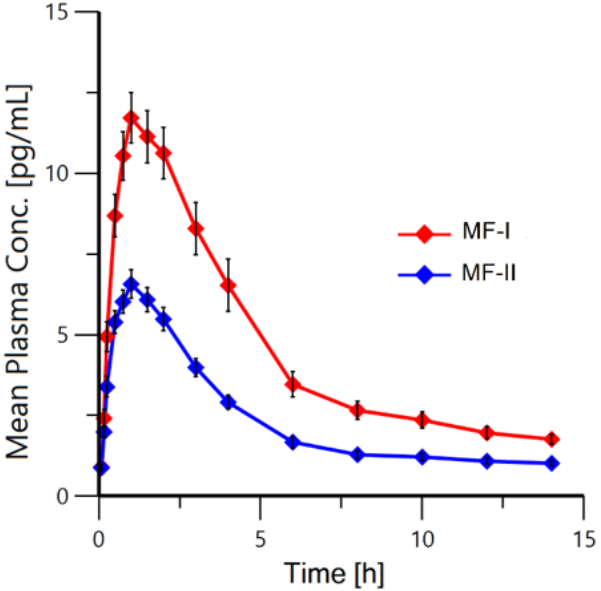


- Charcoal: 5 g at 5 min prior to dosing, then 5, 60, 120 and 180 min after dosing (total dose of 25 g)
- MF dose: 2 actuations into each nostril (i.e., 4 actuations total for ~200 µg dose)
- Administered by experienced clinical personnel

Hochhaus G, et al. *RDD 2022.* Volume 1: 47-54.

Alternative Approaches: Impact of MF PSD on In Vivo Data

A total of 44 healthy volunteers completed both study visits.



Parameter	Arithmetic Mean (SD)	
	MF-I (Dv50 3.17 µm)	**MF-II** (Dv50 5.5 µm)
C_{max} [pg/mL]	13.6 (6.11)	7.34 (2.94)
$AUC_{0\text{-}last}$ [pg/mL*h]	63.4 (36.0)	32.1 (15.5)
$AUC_{0\text{-}inf}$ [pg/mL*h]	86.2 (45.9)	45.8 (22.7)

- **PK study sensitive enough to detect differences in API particle size**
- Formulation with larger particle size (MF-II) showed smaller AUC and smaller C_{max}

Overall, in vitro (MDRS and dissolution) and PK studies were shown to be sensitive to detect differences in API particle size.

Hochhaus G, et al. *RDD 2022.* Volume 1: 47-54.

Alternative Approaches to Demonstrate BE of Nasal Suspensions

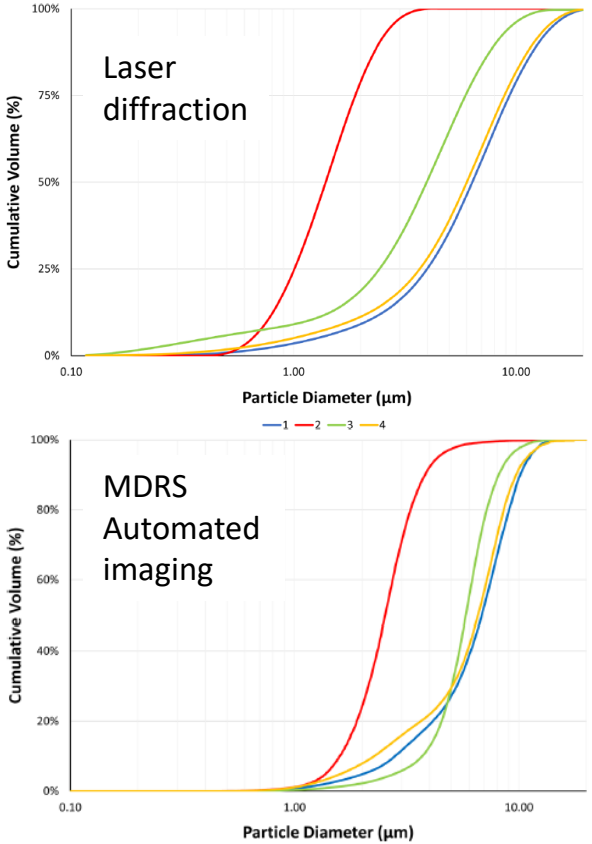
Contract HHSF223201710163C with University of Bath

Objective: To use a combination of techniques to investigate API PSD in nasal suspensions and dissolution rate to characterize test and reference nasal suspensions

- Four batches of MF API were sized by laser diffraction and automated imaging (sizing methodology used by MDRS)

Technique	Batch	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
Laser diffraction (as-received)	1	2.14 (0.05)	6.36 (0.08)	12.57 (0.11)
	2	0.76 (0.01)	1.39 (0.01)	2.42 (0.03)
	3	1.14 (0.01)	3.97 (0.02)	8.11 (0.10)
	4	1.81 (0.05)	6.01 (0.15)	11.94 (0.25)
Automated imaging (as-received)	1	2.81 (0.05)	6.84 (0.50)	10.09 (0.48)
	2	1.63 (0.19)	2.54 (0.24)	3.77 (0.34)
	3	3.69 (0.15)	5.80 (0.04)	8.14 (0.26)
	4	2.60 (1.13)	6.54 (0.23)	9.72 (0.20)

➢ Both sizing techniques resulted in same rank order of the batches: largest Dv50: Batch 1 ≈ Batch 4 > Batch 3 > Batch 2



Farias G, et al. *AAPS J.* 2021; 23(4):73.

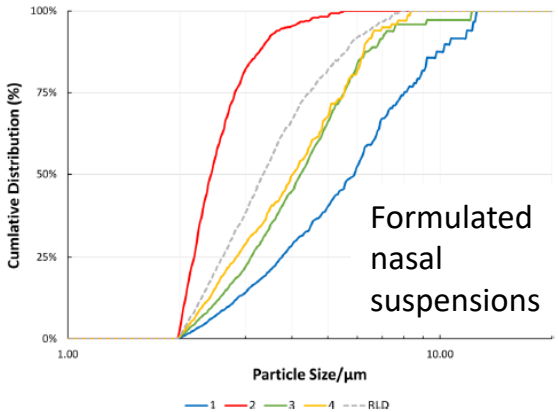
Alternative Approaches: Impact of MF PSD on In Vitro Data

MF batches were formulated to be qualitatively and quantitatively the same as Nasonex®

- In vitro BE tests (single actuation content, droplet size distribution by laser diffraction, spray pattern and plume geometry) were performed with the four formulations

➢ No statistical differences were observed suggesting that MDRS may be necessary to characterize API PSD

MDRS employed to determine the API particle size in the formulated drug products



Technique	Batch	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
MDRS (final product)	1	2.72 (0.29)	5.64 (0.62)	10.26 (1.36)
	2	2.05 (0.01)	2.43 (0.03)	3.41 (0.15)
	3	2.47 (0.20)	4.21 (0.46)	6.60 (0.40)
	4	2.30 (0.01)	4.03 (0.04)	6.33 (0.07)
	Nasonex®	2.28 (0.14)	3.20 (0.92)	5.47 (1.28)

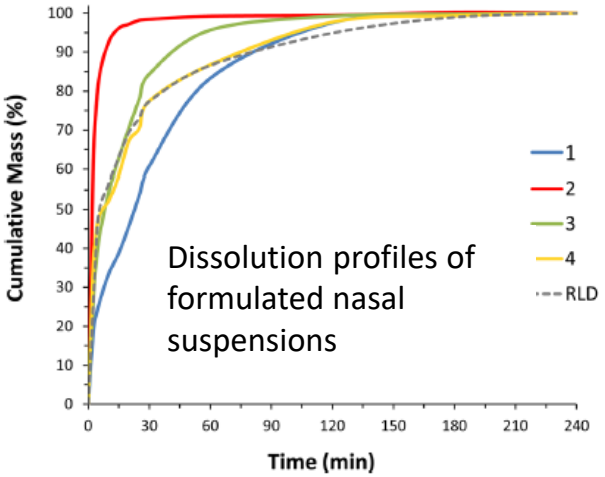
➢ Rank order: largest Dv50 = Batch 1 > Batch 3 ≈ Batch 4 > Batch 2

Farias G, et al. *AAPS J.* 2021; 23(4):73.

Alternative Approaches: Impact of MF PSD on In Vitro Data

Dissolution tests were performed with the USP Apparatus II

- Dissolution media: pH 7.4 phosphate-buffered saline + 2.0% w/v SDS at 37°C



Dissolution profiles of formulated nasal suspensions

- Dissolution tests were able to differentiate formulations with different API particle size
- Dissolution of batch 3 and 4 were similar to Nasonex® based on f2 values >50

Batch	2	3	4	Nasonex®
1	10.98	29.59	32.16	30.72
2	-	21.71	21.10	21.63
3	-	-	54.12	59.03
4	-	-	-	62.36

A relationship was observed between MDRS PSD and dissolution.

Farias G, et al. *AAPS J.* 2021; 23(4):73.

Considerations from Research Findings on BE Demonstration of Nasal Suspensions

- Raman spectroscopy was capable of characterizing API-specific PSD of nasal suspensions
- Dissolution using various systems (USP Apparatus II, USP Apparatus V, Transwell®) were sensitive in detecting differences in API PSD
  - Formulations with a larger API PSD showed slower dissolution
- PK studies were sensitive in detecting differences in API PSD
  - Formulations with a larger API PSD showed smaller AUC and C_{max}

➢ Research supports the ability to characterize drug PSD in nasal suspensions, possibly providing additional methods to complement the current alternative approach recommendations in PSGs on nasal suspension products

Challenge Question #1

Which of the following statements is NOT true?

A. Comparative clinical endpoint (CCEP) BE, PK BE, and in vitro BE studies all provide indirect evidence of equivalent local delivery.

B. The weight-of-evidence approach to demonstrate BE of nasal suspension products includes in vitro studies, in vivo PK studies and a CCEP BE study or an alternative approach.

C. The recommendations for demonstration of BE for all nasal products include in vitro and in vivo studies.

D. The alternative approach to the CCEP BE study was recommended following FDA approval of the first generic mometasone furoate nasal spray product.

Challenge Question #2

The recommended comparative clinical endpoint BE study provides evidence of equivalent…?

A. Local delivery.

B. In vitro performance.

C. Systemic exposure.

D. Drug formulation.

Summary

- The recommendations for demonstration of BE of nasal suspension products relies on a weight-of-evidence approach which includes in vitro studies, in vivo PK studies and a CCEP BE study
- In vivo studies were recommended because of an inability to adequately characterize drug particle size distribution in nasal sprays
- An alternative to the CCEP BE study was provided due to recent advancements in analytical methods that allow for ingredient-specific particle size measurements in nasal suspension products
- Recent findings from ORS research may provide additional methods to complement the current alternative approach recommendations provided in product-specific guidances on nasal suspension products

Acknowledgements

- FDA/CDER/OGD/ORS
  - Bryan Newman, PhD
  - Elizabeth Bielski, PhD
  - Liangfeng Han, MD, PhD
  - Darby Kozak, PhD
  - Markham Luke, MD, PhD
  - Lei Zhang, PhD
  - Robert Lionberger, PhD
- FDA/CDER/OPQ/OTR
  - Jason Rodriguez, PhD
  - Changning Guo, PhD
- FDA/CDER/OPQ/ONDP
  - Renishkumar Delvadia, PhD
- FDA/CDER/OGD/OSCE
  - Kimberly Witzmann, MD
  - Denise Conti, PhD
- FDA/CDER/OTS/OCP
  - Sneha Dhapare, PhD
  - Bhawana Saljua, PhD
- FDA/CDER/OSE/OMEPRM
  - Oluwamurewa Oguntimein, PhD
- University of Florida
  - Guenther Hochhaus, PhD
  - Juergen Bulitta, PhD
- University of Bath and Nanopharm
  - Jag Shur, PhD
  - Robert Price, PhD

U.S. FOOD & DRUG ADMINISTRATION

Questions?

Susan Boc
Scientific Reviewer
Division of Therapeutic Performance, Office of Research and Standards
CDER | U.S. FDA


FDA
U.S. FOOD & DRUG
ADMINISTRATION

Resources

- FDA product-specific guidance webpage
- FDA draft guidance for industry, *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003)
- Vo A, Feng X, Smith WC, Zhu D, Patel M, Kozak D, Wang Y, Zheng J, Ashraf M, Xu X. Analyzing ophthalmic suspension particle size distributions using laser diffraction: Placebo background subtraction method. *Int J Pharm* 2021, 598:120401.
- Liu Q, Absar M, Saluja B, Guo C, Chowdhury B, Lionberger R, Connor DP, Li BV. Scientific Considerations for the Review and Approval of First Generic Mometasone Furoate Nasal Suspension Spray in the United States from the Bioequivalence Perspective. *AAPS J* 2019, 21(2):14.
- Thomas BJ, Absar M, Delvadia R, Conti DS, Witzmann K, Guo C. Analytical method development for characterizing ingredient-specific particle size distributions of nasal spray suspension products. *J Pharm Sci* 2021,110(7):2778-2788.
- Farias G, Shur J, Price R, Bielski E, Newman B. A Systematic Approach in the Development of the Morphologically-Directed Raman Spectroscopy Methodology for Characterizing Nasal Suspension Drug Products. *AAPS J* 2021, 23(4):73.
- Hochhaus G, et al. Evaluating Particle Size Differences of Suspension-Based Nasal Sprays Through In Vitro and Pharmacokinetic Approaches. *Respiratory Drug Delivery 2022*. Volume 1, 2022:47-54.