Complex Nasal Suspension PSGs: Utilization of Newly Recommended In Vitro Only Bioequivalence Option

SBIA 2023—Advancing Generic Drug Development: Translating Science to Approval

Day 1, Session 2: Noteworthy Guidances for Nasal Suspension and Inhalation Products

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Learning Objectives

- Explain the rationale for the revision of product-specific guidances (PSGs) on locally-acting nasal spray suspension products
- Describe the two options to establish bioequivalence (BE) for locally-acting nasal spray suspension products
- List the newly recommended in vitro studies and the key considerations for each study

Product-Specific Guidance Revisions

GDUFA-funded research[1-3] supported the revision of nine PSGs on locally-acting nasal spray suspension products

- Raman spectroscopy was capable of characterizing drug-specific particle size distribution (PSD) of nasal suspensions
- Dissolution studies using various systems (USP Apparatus 2, USP Apparatus 5, Transwell®) were sensitive in detecting differences in drug PSD
- Pharmacokinetic (PK) studies were sensitive in detecting differences in drug PSD

Available at FDA's PSG webpage[4]:

Azelastine Hydrochloride; Fluticasone Propionate Nasal Spray, Metered (May 2023)
Fluticasone Furoate Nasal Spray, Metered (May 2023)
Fluticasone Propionate Nasal Spray, Metered (NDA 020121, May 2023)
Mometasone Furoate Nasal Spray, Metered (NDA 020762, May 2023)
Beclomethasone Dipropionate Monohydrate Nasal Spray, Metered (Aug 2023)
Budesonide Nasal Spray, Metered (Aug 2023)
Ciclesonide Nasal Spray, Metered (Aug 2023)
Mometasone Furoate; Olopatadine Hydrochloride Nasal Spray, Metered (Aug 2023)
Triamcinolone Acetonide Nasal Spray, Metered (Aug 2023)

GDUFA: Generic Drug User Fee Amendments; USP: United States Pharmacopeia

PSG Recommendations on Nasal Spray Suspension Products

Bioequivalence (BE) recommendations for nasal spray suspension products include two options based on qualitative (Q1) and quantitative (Q2) sameness of test (T) and reference listed drug (RLD) product formulations

Option 1: In vitro BE studies for Q1 and Q2 formulations

- **Drug Particle Size Distribution**
- **Dissolution**

Option 2: In vitro and in vivo BE studies for non Q1 and Q2 formulations

- Single Actuation Content
- Droplet Size Distribution by Laser Diffraction
- Drug in Small Particles/Droplets
- Spray Pattern
- Plume Geometry
- Priming and Repriming

- Comparative PK with fasting, two-way crossover design in healthy subjects
- Comparative Clinical Endpoint

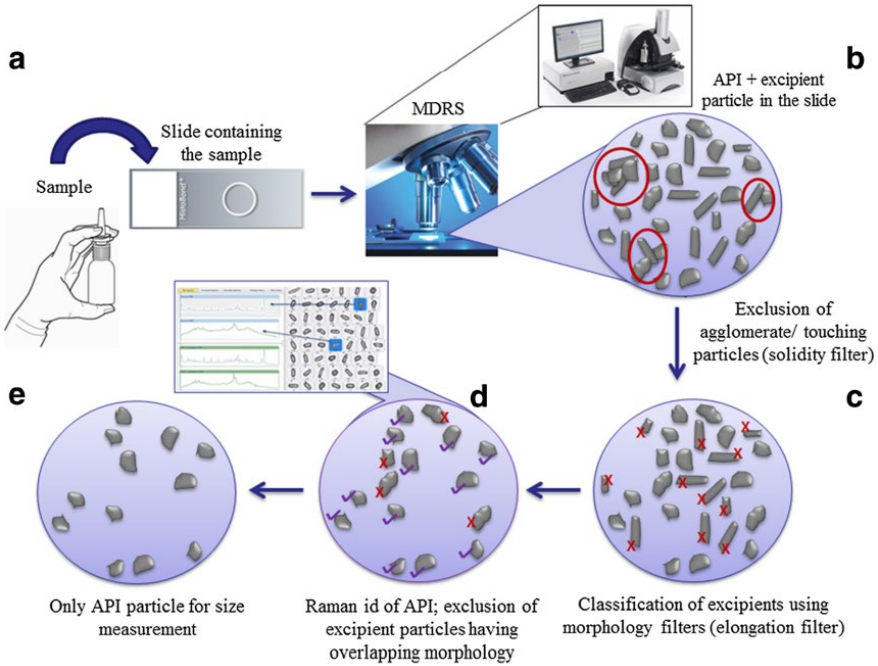
Newly Recommended In Vitro BE Studies

Drug PSD

Considerations for Drug PSD Characterization

*Use an **optimized and validated analytical method**, e.g., morphologically-directed Raman spectroscopy (MDRS)*

- MDRS is an integrated platform that measures particle morphological characteristics using its microscopic component, and performs chemical identification via Raman spectroscopy
- Basic measurement procedure includes[5]:
  a. Sample preparation
  b. Particle imaging and morphology analysis
  c. Morphology filter selection
  d. Identification using Raman spectra
  e. Size measurement



API = Active Pharmaceutical Ingredient

Considerations for Drug PSD Characterization Using MDRS – Sample Preparation

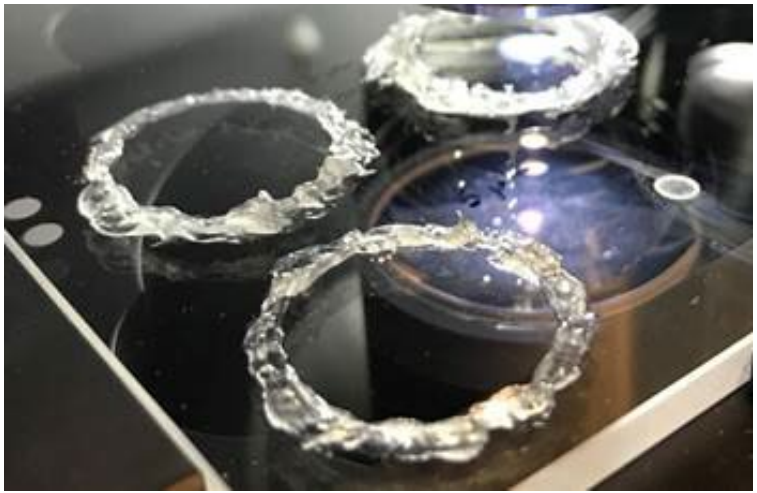
*Samples should be prepared to ensure that **drug is in its suspended state** post-actuation*

- Dry dispersion may cause particle aggregation upon solvent evaporation

➢ Example Wet Dispersion Sample Method for MDRS[1,2,6]:

1. Shake and prime nasal spray
2. Collect optimized number of actuations into a glass vial
3. Pipet a set volume of the collected sample onto a microscope slide and cover with a coverslip
4. Seal with petroleum jelly (or similar substance) along edge of coverslip to prevent evaporation
5. Let sample rest to allow particles to settle before analysis

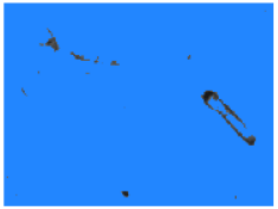
❖ Ideally, touching particles should be <5% of total particles



Considerations for Drug PSD Characterization Using MDRS – Particle Imaging and Analysis

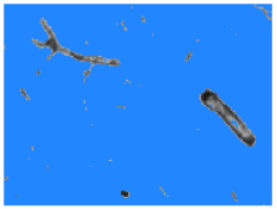
*Provide **optimization and validation data** for particle imaging settings*

Threshold level[7]:



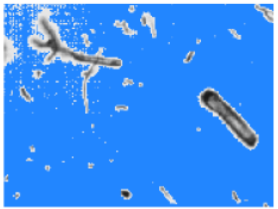
Threshold = 100

Too low, particles begin to disappear.



Threshold = 175

Aim for a thin gray border around the edge of the particles and a complete perimeter.

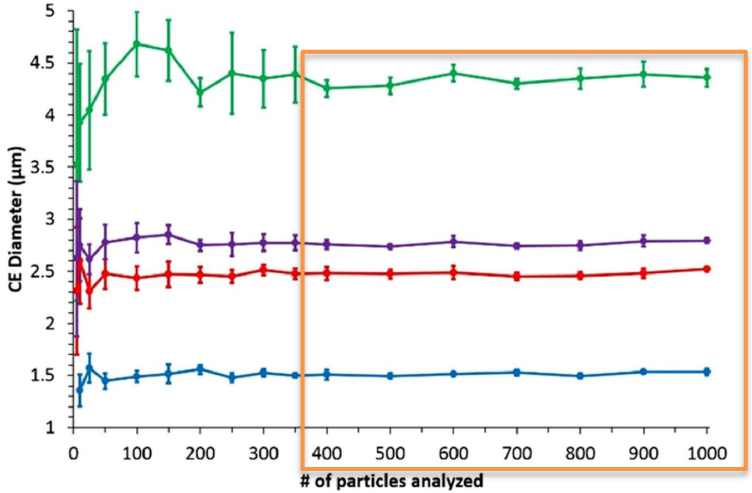


Threshold = 235

Too high, particles are oversized and the background starts to count.

Minimum number of particles[1]:

Different particle counts should be compared to determine minimum number of particles for reliable measurements



CE = Circular equivalent

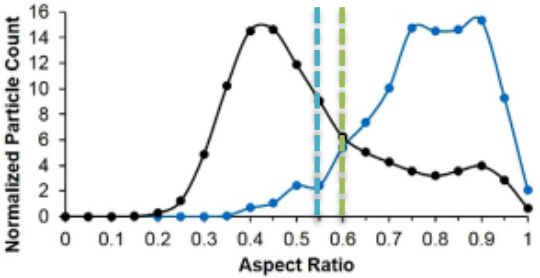
Considerations for Drug PSD Characterization Using MDRS – Morphology Filter Selection[1]

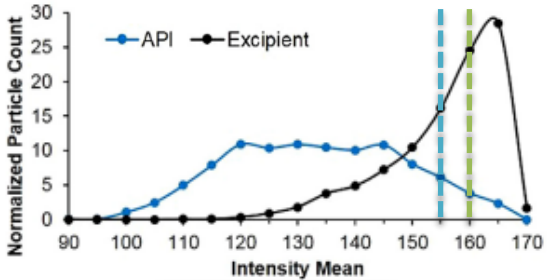
*Provide **optimization and validation data** for morphology filter selection*

- Reduce total analysis time by using analytical filters prior to Raman measurement
- Select filters and appropriate cut-off values to eliminate as many excipient particles as possible while minimizing the number of drug particles not included in the analysis

➢ Example with Nasonex® as model drug product:

- Retain at least 85% of drug particles





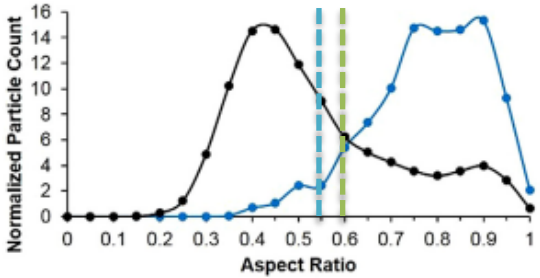
	No Filters	AR > 0.60IM < 150	AR > 0.60IM < 155	AR > 0.60IM < 160	AR > 0.55IM < 155	AR > 0.50IM < 150
API Particle Count	1335	1035	1120	1170	1170	1110
Excipient Particle Count	9500	470	830	1380	1070	840
Total Particle Count	10835	1505	1950	2550	2240	1950
% API Particles	12.3%	68.8%	57.4%	45.9%	52.2%	56.9%
# API Particles Removed	0	300	215	165	165	225
# Excipient Particles Removed	0	9030	8670	8120	8430	8660
% API Particles Retained	100%	77.5%	83.9%	87.6%	87.6%	83.1%
% Excipient Particles Removed	0%	95.0%	91.3%	85.5%	88.7%	91.2%

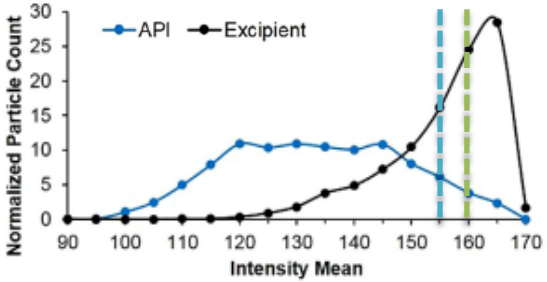
AR = Aspect Ratio
IM = Intensity Mean

Considerations for Drug PSD Characterization Using MDRS – Morphology Filter Selection cont.[1]

*Provide **optimization and validation data** for morphology filter selection*

- Validation of the filter selections should be checked by comparing drug PSD results before and after applying filters (ideally, < 3% difference)





Summary of drug PSD data before and after application of aspect ratio (AR) and intensity mean (IM) morphology filters.

	No Filters	AR > 0.60IM < 150	AR > 0.60IM < 155	AR > 0.60IM < 160	AR > 0.55IM < 155	AR > 0.50IM < 150
D_{mean} (μm)	3.00	3.10 (3.3%)	3.03 (1.0%)	2.98 (0.7%)	3.06 (2.0%)	3.15 (5.0%)
D10 (μm)	1.71	1.90 (11%)	1.83 (7.0%)	1.75 (2.3%)	1.84 (7.6%)	1.91 (12%)
D50 (μm)	2.60	2.69 (3.5%)	2.61 (0.4%)	2.56 (1.5%)	2.64 (1.5%)	2.73 (5.0%)
D90 (μm)	4.60	4.63 (0.7%)	4.60 (0.0%)	4.54 (1.3%)	4.61 (0.2%)	4.67 (1.5%)
Span	1.11	1.01 (9.0%)	1.06 (4.5%)	1.09 (1.8%)	1.05 (5.4%)	1.01 (9.0%)

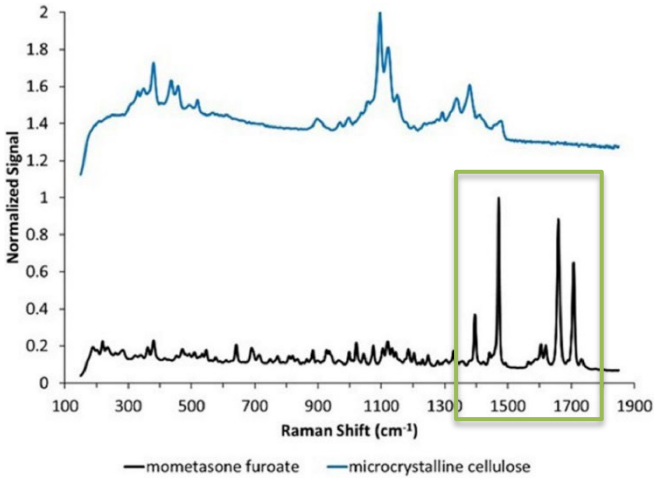
Considerations for Drug PSD Characterization Using MDRS – Identification Using Raman Spectra[1,2]

*Provide **optimization and validation data** for Raman spectroscopy settings*

- The longer the exposure time, the better the Raman spectrum quality – balance the quality of the Raman measurement and total experiment time
- Comparing collected spectra to reference library within the spectral correlation range specific for the drug of interest should improve signal-to-noise ratio

➢ Example Raman spectra of drug (mometasone furoate, MF) and excipient (microcrystalline cellulose, MCC):

  - Four signature MF peaks with no overlapping MCC peaks in 1350-1750 cm^{-1} range; thus, selected as spectral correlation range for classification of drug particles

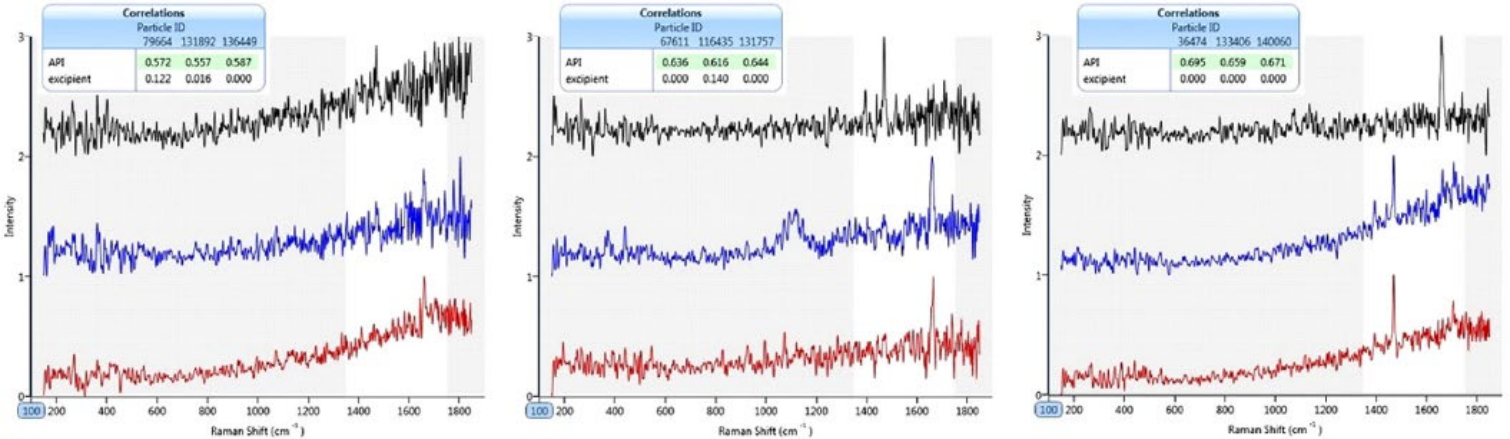


Example Raman spectra of chemical standards[1]

Considerations for Drug PSD Characterization Using MDRS – Identification Using Raman Spectra cont.[1]

*Provide **optimization and validation data** for Raman spectroscopy settings*

- Determine the cutoff spectral correlation score for drug particle classification based on evaluation of particle Raman spectra for limit of detection
- Example comparison of particle spectra with drug spectral correlation scores[1]:
  - Selection criteria: at least one of the four drug peaks had to be observed with acceptable S/N (>3)
  - A correlation score of > 0.60 was selected for identifying drug



Considerations for Drug PSD Characterization Using MDRS – Orthogonal Methods

*An **orthogonal method may be required** if the selected methodology is not sensitive to measure particles beyond a certain size range*

- With MDRS, the lowest detectable size for the Raman component is 1 µm,[7] which may require use of an orthogonal method to assess submicron drug particles

➢ **Case Study** – first approved Mometasone Furoate Nasal Spray referencing Nasonex®:

As published in Liu et al., 2013[5], the applicant submitted the following data:

- Drug PSD in the drug product using MDRS
- Particle size data up to 0.5 µm using Morphologi G3 instrument (lacks the Raman component)
- Laser diffraction data demonstrating that % particles below 0.5 µm was <1% for both T and R products

Given the totality of evidence, MDRS was deemed **acceptable** to compare drug PSD between T and RLD Mometasone Furoate Suspension Spray products

Newly Recommended In Vitro BE Studies

Dissolution

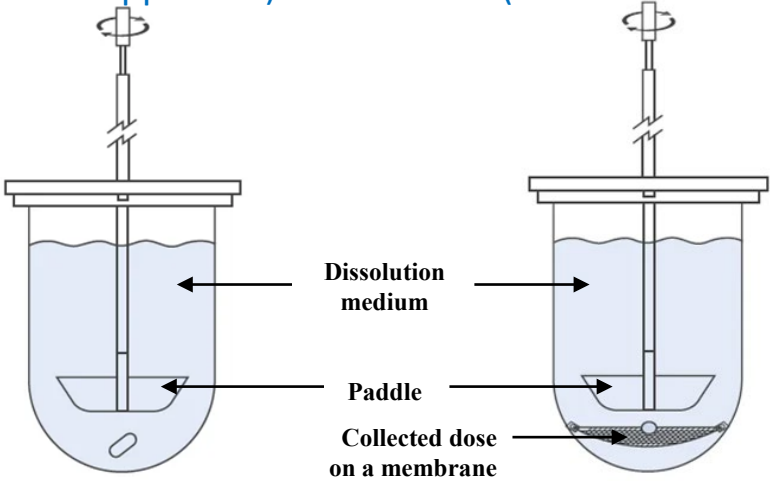
Considerations for Dissolution Measurements – Dissolution Apparatus

*An **appropriate apparatus** (e.g., USP <711> Apparatus 2, USP <724> Apparatus 5, or Transwell system) may be used to determine dissolution measurements*

Sink Conditions:

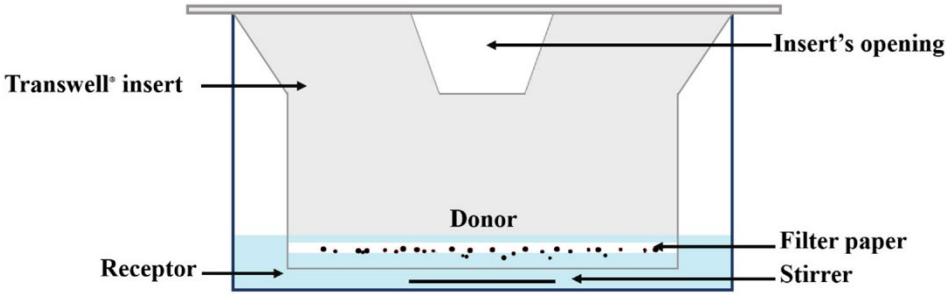
USP <711> Apparatus 2
(Paddle Apparatus)[8]

USP <724> Apparatus 5
(Paddle over Disk)[8]



Non-Sink Conditions:

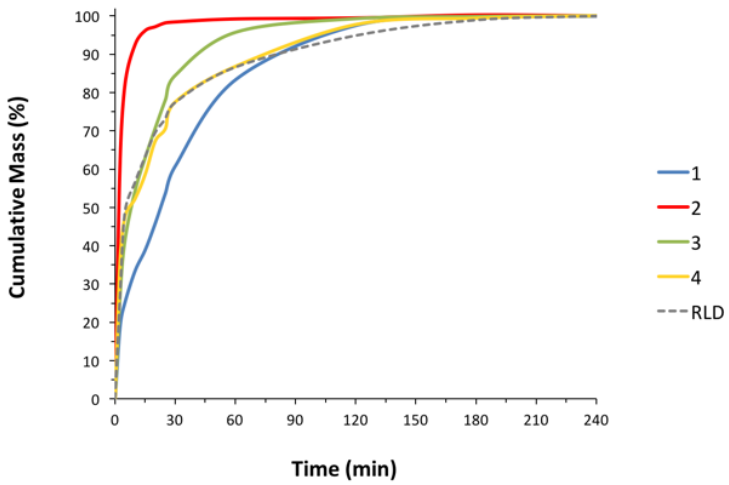
Transwell® System[9]



Considerations for Dissolution Measurements – Method Development and Validation

*Use a **sufficiently developed and validated method** to support its sensitivity in detecting differences in performance between T and RLD products*

- Dissolution media selection should be guided by solubility investigations and be optimized to be discriminatory
- Stability of the drug substance should be carried out in the selected dissolution media alone and in the formulated drug product
- Enough time points should be selected to adequately characterize the ascending and plateau phases of the dissolution curve



Example dissolution profile comparison[2]:
USP Apparatus 2, pH 7.4 phosphate-buffered saline with 2.0% w/v sodium dodecyl sulfate at 37°C

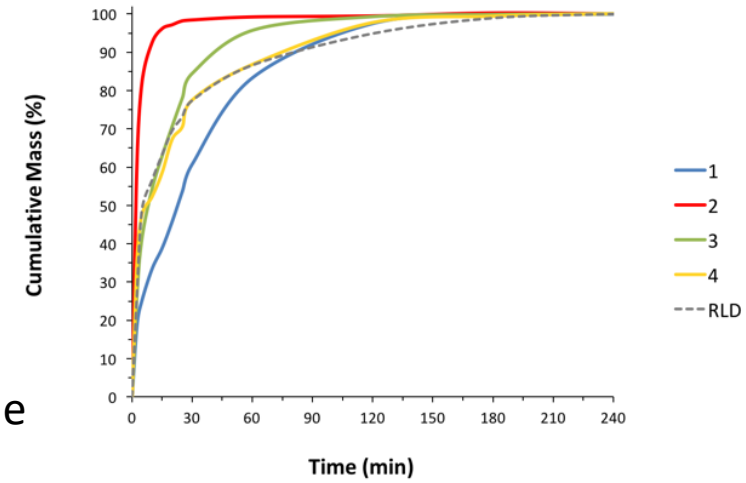
Considerations for Dissolution Measurements – Method Validation cont.

*Demonstrate **discriminatory ability** (e.g., ability to detect meaningful differences in formulation or manufacturing processes, such as difference in drug particle size)*

- The goal is to understand release mechanisms and determine whether the dissolution procedure can show changes in critical quality attributes of the drug product
  - Formulations intentionally manufactured with meaningful variations for the most relevant critical manufacturing variable or stressed samples

➢ Example of formulations with different drug particle size[2]:

Batch	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
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)



Example dissolution profile comparison[2]:
USP Apparatus 2, pH 7.4 phosphate-buffered saline with 2.0% w/v sodium dodecyl sulfate at 37°C

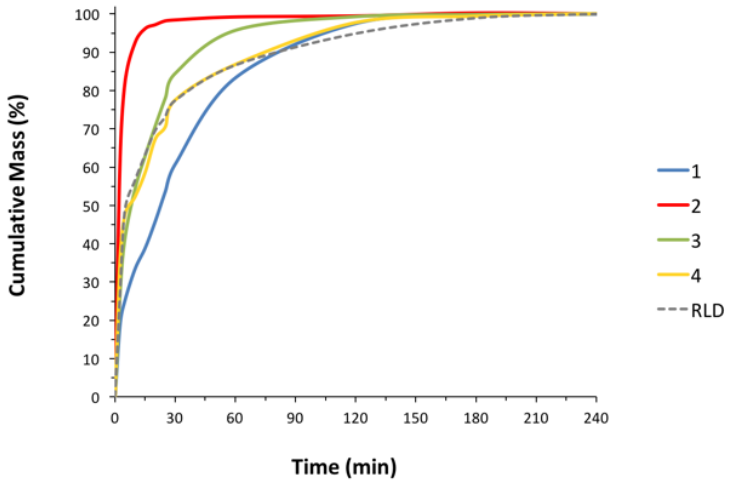
Considerations for Dissolution Measurements – BE Assessment

*Comparative analysis of dissolution profiles should be established using an **appropriate statistical method**, e.g., model independent approach using similarity factor (f2)*

- f2 analysis allows for comparison of the dissolution profile rather than single-point dissolution comparisons
  - Other statistical methodology may be used by providing appropriate statistical rationale with adequate justification

➢ Example of f2 analysis of the average dissolution profile for the first 60 minutes:

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



Example dissolution profile comparison[2]:
USP Apparatus 2, pH 7.4 phosphate-buffered saline with 2.0% w/v sodium dodecyl sulfate at 37°C

Summary

- Based on GDUFA-funded research, PSGs for locally-acting nasal spray suspension products were revised to include **two BE options**:
  - Option 1 is an **in vitro only** pathway to demonstrate BE for T and RLD product formulations that are Q1 and Q2 the same
  - Option 2 (**in vitro and in vivo studies**) provides a pathway for T and RLD product formulations that are not Q1 and Q2 the same to demonstrate BE
- Key considerations for **Drug PSD characterization using MDRS**: sample preparation, particle imaging and analysis, morphology filter selection, identification using Raman spectroscopy
- Key considerations for **Dissolution studies**: dissolution apparatus selection, method development and validation, BE assessment

Challenge Question #1

How many in vitro bioequivalence studies are recommended when the test product formulation is qualitatively and quantitatively the same as the RLD formulation (Option 1):

A. 6

B. 7

C. 8

D. 9

Challenge Question #2

Which of the following statements is NOT true?

A. There are no in vivo studies recommended in the product-specific guidances on locally-acting nasal spray suspension products.

B. Sample preparation for Drug PSD characterization should ideally be as a wet dispersion to maintain the drug in its suspended state.

C. In vitro and in vivo BE studies are recommended for test product formulations that are not Q1 and Q2 the same as the RLD formulation.

D. Recommendations for Dissolution studies include the use of USP and non-USP dissolution apparatuses.

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- University of Bath and Nanopharm
  - Jag Shur
  - Robert Price


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Resources

1. 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.

2. 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.

3. 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.

4. FDA product-specific guidance webpage

5. 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

Resources

6. Holtgrewe N. Alternative Bioequivalence Approach Using Morphologically-Directed Raman Spectroscopy (MDRS) on Nasal Spray Suspensions. *Presentation at FDA and Center for Complex Generics (CRCG) Workshop on: Considerations for and Alternatives to Comparative Clinical Endpoint and Pharmacodynamic Bioequivalence Studies for Generic Orally Inhaled Drug Products.* Apr 21, 2023. Rockville, MD.

7. Malvern Panalytical webpage on Morphologi 4-ID

8. Antech Solutions webpage Introduction to Dissolution Testing

9. Amini E, Kurumaddali A, Bhagwat S, Berger SM, Hochhaus G. Optimization of the Transwell® System for Assessing the Dissolution Behavior of Orally Inhaled Drug Products through In Vitro and In Silico Approaches. Pharmaceutics. 2021, 13(8),1109. https://doi.org/10.3390/pharmaceutics13081109