Recommendations for Demonstrating Bioequivalence of Nasal Sprays: Scientific Thinking and Regulatory Research

IPAC-RS: 2025 Nasal Innovation Forum

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Outline

- Overview of nasal drug products (NDPs) and complexities related to generic development
- FDA-approved nasal products and current recommendations to demonstrate bioequivalence (BE)
- Describe the option-based approach to establish BE for locally acting nasal spray suspension products and the research supporting the current recommendations
- Other regulatory research on NDPs

Nasal Drug Delivery

Nasal Sprays

- Typically pump-driven but propellant-driven and breath-aided products exist
- Aqueous and non-aqueous formulation within bottle/vial
- Active ingredient can be suspended or in solution
- Typically deposit as formulation droplets

Nasal Aerosols

- Propellant-driven aerosolization
- Non-aqueous formulation in canister
- Active ingredient in solution
- Typically deposit as dry particles or semi-dry particles upon evaporation of volatile components; may be dependent on formulation

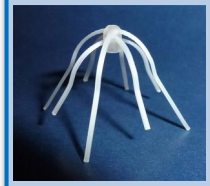
Nasal Powders

- Diverse designs (e.g., air pump, plunger, patient breath-driven aerosolization,)
- Solid blend of active ingredient particles/agglomerates with or without excipients
- Deposit 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
- Active ingredient in solution or suspension
- Drug is directly applied to the nasal surface

Nasal Implants

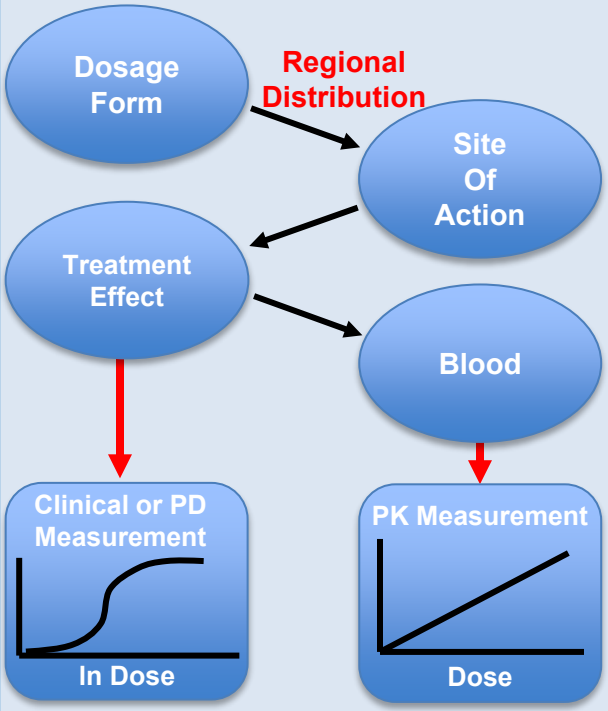


- Physician-applied using a hand-held delivery system
- Implant comprised of PLGA/PLCL with a coating of active ingredient embedded within a PLGA/PEG bioabsorbable polymer matrix
- Drug slowly released to the ethmoid sinus

* images from google images; search terms: “flonase”, “qnasal”, “natesto”, “onzetra”, “sinuva”

Complexities 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

- Active ingredient state
- Physicochemical properties
- Types and amounts of inactive ingredients

Active ingredient particles

Inactive ingredient particles

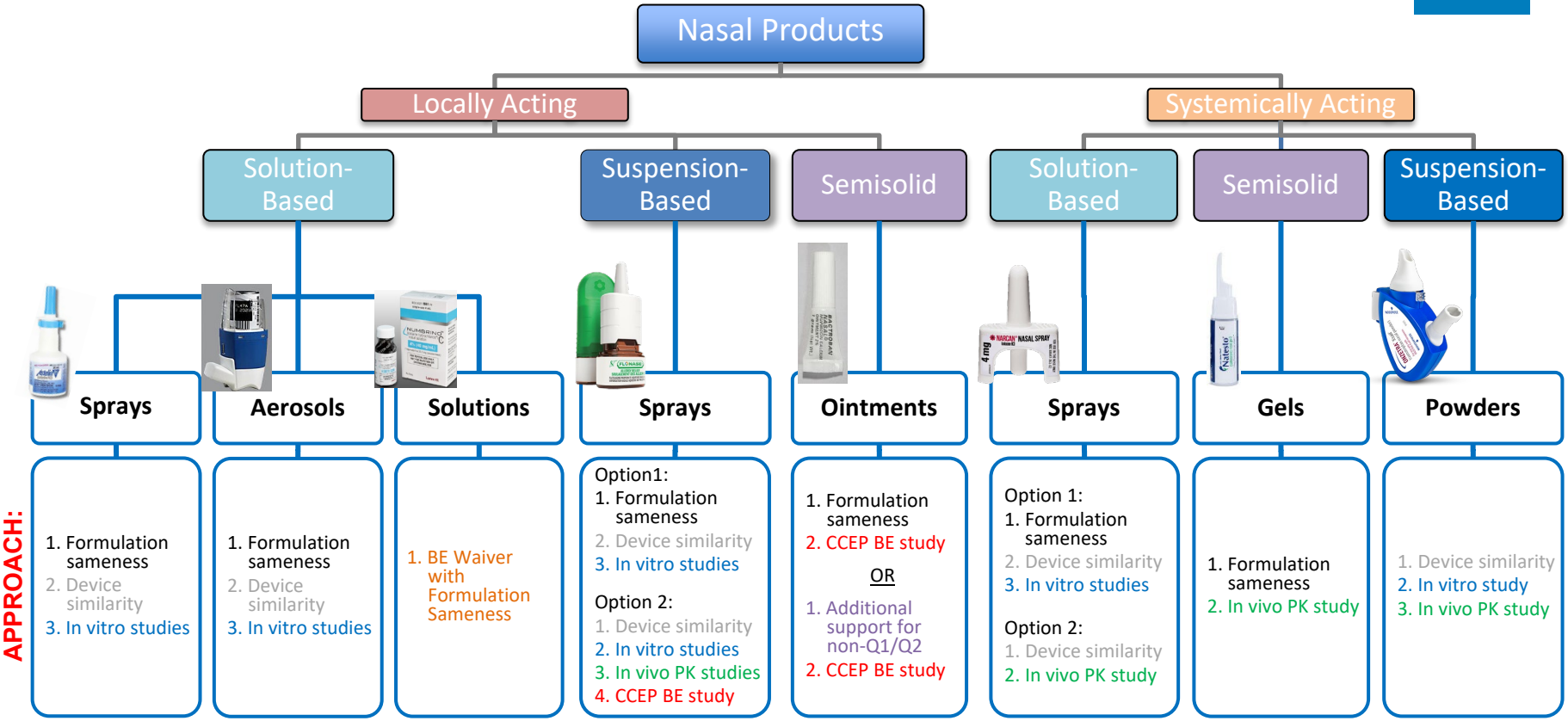
Diluent +/- solubilized API/inactive ingredients

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

*For locally-acting products

PK: pharmacokinetic
PD: pharmacodynamic

FDA-approved NDPs



CCEP: Comparative clinical endpoint

FDA-approved NDPs

Nasal Products

Locally Acting

- Solution-Based
  - Sprays
    - 1. Formulation sameness
    - 2. Device similarity
    - 3. In vitro studies
  - Aerosols
    - 1. Formulation sameness
    - 2. Device similarity
    - 3. In vitro studies
  - Solutions
    - 1. BE Waiver with Formulation Sameness
- **Suspension-Based**
  - **Sprays**
    - Option1:
      1. Formulation sameness
      2. Device similarity
      3. In vitro studies

      Option 2:
      1. Device similarity
      2. In vitro studies
      3. In vivo PK studies
      4. CCEP BE study
- Semisolid
  - Ointments
    - 1. Formulation sameness
    - 2. CCEP BE study

      OR

      1. Additional support for non-Q1/Q2
      2. CCEP BE study

Systemically Acting

- Solution-Based
  - Sprays
    - Option 1:
      1. Formulation sameness
      2. Device similarity
      3. In vitro studies

      Option 2:
      1. Device similarity
      2. In vivo PK study
- Semisolid
  - Gels
    - 1. Formulation sameness
    - 2. In vivo PK study
- Suspension-Based
  - Powders
    - 1. Device similarity
    - 2. In vitro study
    - 3. In vivo PK study

BIOEQUIVALENCE APPROACH:

www.fda.gov

CCEP: Comparative clinical endpoint

BE Recommendations on Nasal Spray Suspension Products

Product-specific guidance (PSG) recommendations for nasal spray suspension products include two options based on formulation sameness of test (T) and reference standard (RS) product formulations

Option 1: In vitro BE studies for formulations with no difference in inactive ingredients (e.g., Q1 and Q2 the same)

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

Option 2: In vitro and in vivo BE studies*

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

Q1: Qualitative sameness;
Q2: Quantitative sameness

* Option 2 is ***not*** formulation restricted; Q1/Q2 and non-Q1/Q2 formulations are applicable

Research Supporting PSG Recommendations

GDUFA-funded research[2-4] supported the revision of PSGs on locally acting nasal spray suspension products

- Morphologically directed Raman spectroscopy (MDRS) 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

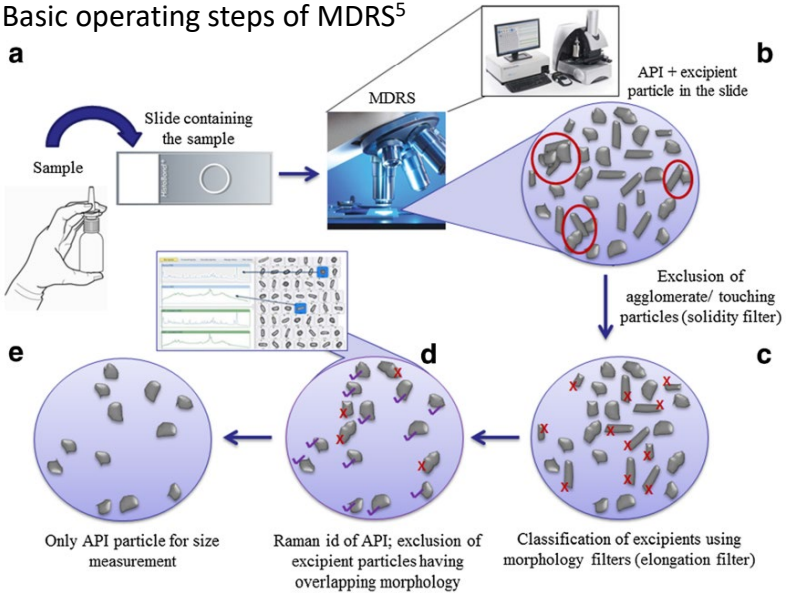
GDUFA: Generic Drug User Fee Amendments;
USP: United States Pharmacopeia

Drug PSD Characterization with MDRS

Internal collaboration with the Office of Pharmaceutical Quality Research (OPQR)

Objective: To develop a robust and reliable MDRS method for characterizing drug particle size in FDA-approved nasal spray suspension drug products[2]

Basic operating steps of MDRS[5]



- Method development procedure included 5 steps:
  1. Sample preparation
  2. Particle imaging and morphology analysis
  3. Morphology filter selection
  4. Identification using Raman spectra
  5. Size measurement

➢ Product-specific experimental parameters were determined for each of the six commercially available products.

API = Active Pharmaceutical Ingredient

In Vitro and PK Sensitivity in Detecting Drug PSD Differences

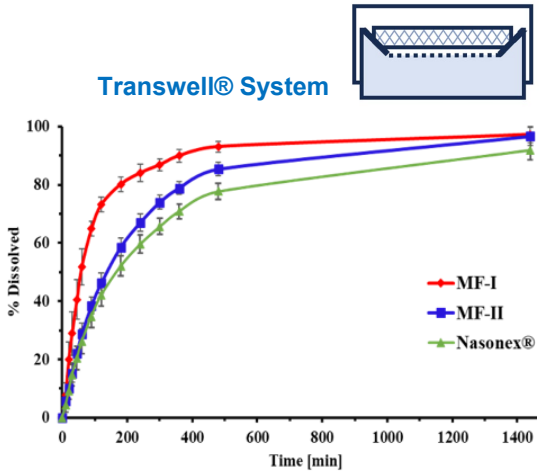
Contract HHSF223201310220C with University of Florida; Contract 75F40120C00036 with Nanopharm

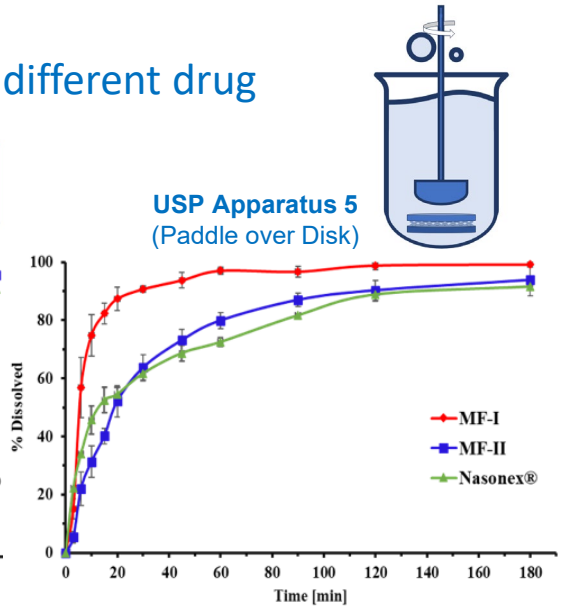
Objective: Evaluate whether selected in vitro and PK studies would be able to differentiate between suspension-based nasal spray formulations that differ in drug PSD[3]

- Mometasone furoate (MF) nasal suspensions were manufactured to be Q1 and Q2 the same as Nasonex® but have different Dv50 values

➢ MDRS and dissolution tests able to differentiate formulations with different drug particle size

Nasal Formulation	MDRS Dv50 [µm]	USP Apparatus V		Transwell®	
		MDT (SD) [h]	VMD (GSD) [µm]	MDT (SD) [h]	VMD (GSD) [µm]
MF-I	3.17	0.14 (0.02)	5.55 (1.44)	1.67 (0.15)	9.05 (2.12)
MF-II	5.50	0.56 (0.06)	10.42 (1.76)	3.58 (0.33)	20.84 (1.82)
Nasonex®	3.20	0.52 (0.06)	9.12 (2.56)	4.64 (0.53)	23.68 (2.08)



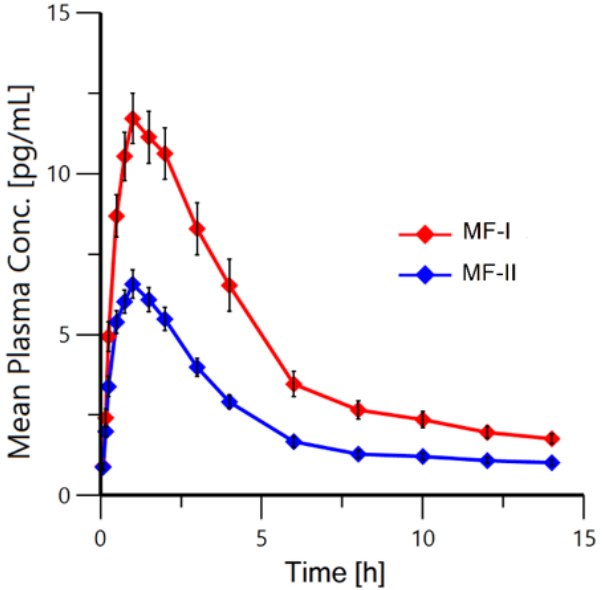


MDT: Mean dissolution time
VMD: Volume median diameter

In Vitro and PK Sensitivity in Detecting Drug PSD Differences

Contract HHSF223201310220C with University of Florida; Contract 75F40120C00036 with Nanopharm[3]

- A PK study was performed with the two manufactured batches



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)

- Formulation with larger particle size (MF-II) showed smaller AUC and smaller C_{max}

➢ PK study sensitive enough to detect differences in drug particle size

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

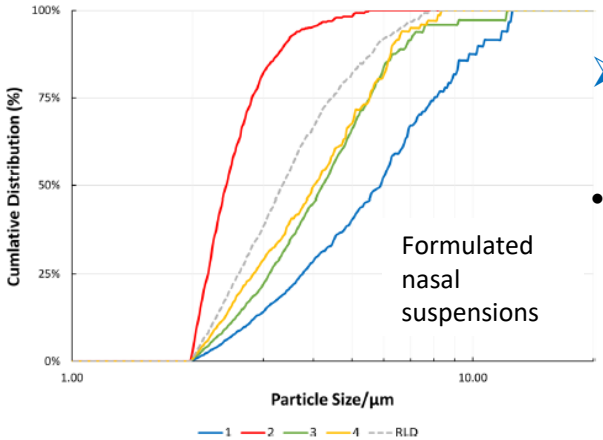
In Vitro Sensitivity in Detecting Drug PSD Differences

Contract HHSF223201710163C with University of Bath

Objective: To use a combination of techniques to investigate drug PSD in nasal suspensions and dissolution rate to characterize test and reference nasal suspensions[4]

- Four MF batches were formulated into nasal suspensions to be Q1 and Q2 the same as Nasonex®

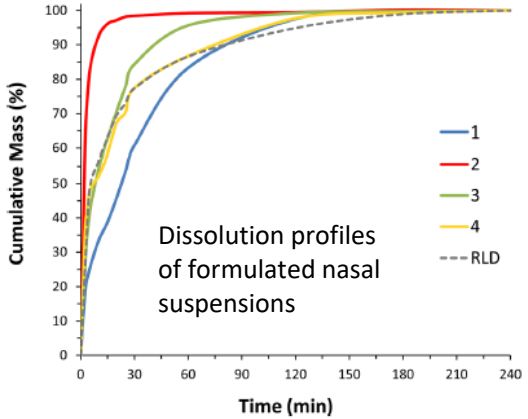
Technique	Batch	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)
MDRS (final product)	1	2.72 (0.29)	5.64 (0.62)	10.26 (1.36)
	2	2.05 (0.01)	2.43 (0.03)	3.41 (0.15)
	3	2.47 (0.20)	4.21 (0.46)	6.60 (0.40)
	4	2.30 (0.01)	4.03 (0.04)	6.33 (0.07)
	Nasonex®	2.28 (0.14)	3.20 (0.92)	5.47 (1.28)



➢ Dissolution tests were able to differentiate formulations with different drug particle size

- Dissolution of batches 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.

Other GDUFA-funded ORS Research on NDPs

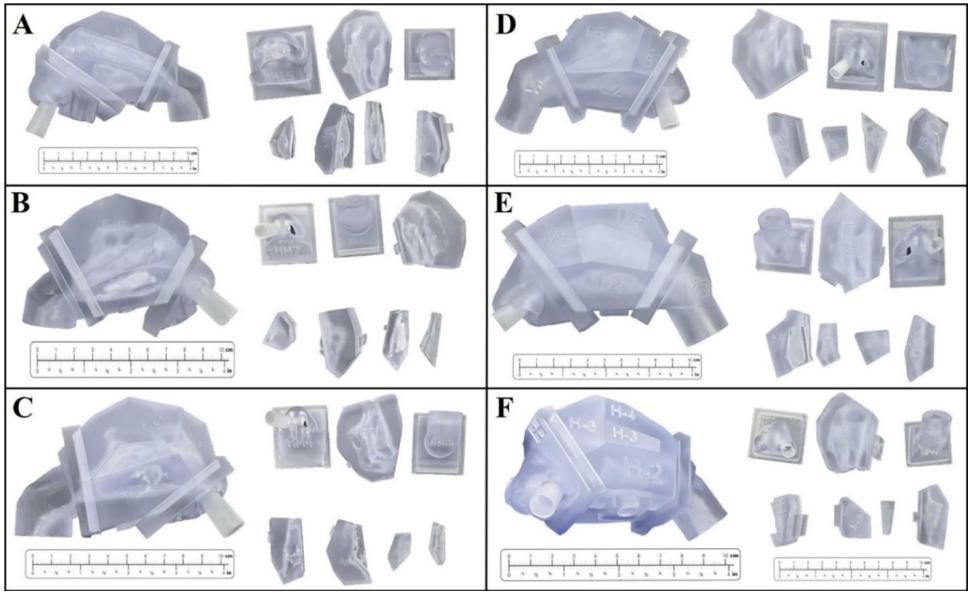
In Vitro Nasal Deposition

Contracts HHSF223201810144C and 75F40120C00172 with Virginia Commonwealth University (VCU)

Objective: To develop two sets of nasal models for adult and pediatric subjects to capture the intersubject variability of regional deposition following nasal administration of corticosteroids[6]

- Nasal airway replicas were developed using computed tomography (CT) images of adults 21-75 years old and children 2-11 years old
  - In general, posterior region deposition was higher for pediatric subjects
  - Population bioequivalence analysis results suggested that anatomical intersubject variability may be impactful for different products

- The use of nasal models show promise for product development
- Use in a regulatory setting requires further evaluation and research

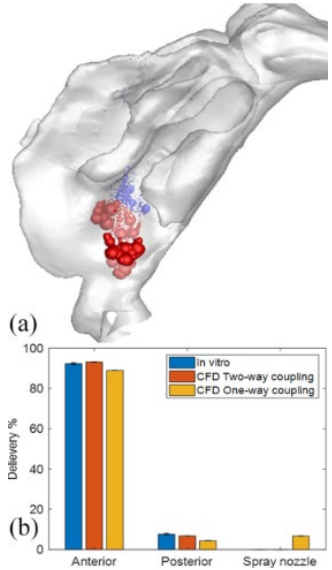


Low, medium, and high deposition of pediatric (A, B, and C, respectively) and adult (D, E, and F, respectively) nasal airway models developed using CT scans

In Vitro Tests and Regional Deposition

Contracts HHSF223201810144C and 75F40120C00172 with Virginia Commonwealth University (VCU)

- Computational fluid dynamics (CFD) model developed by VCU to determine relationships between regional deposition and in vitro BE test metrics[7]



(a) Flonase Sensimist spray droplet deposition locations. (b) comparison of the deposition predictions with in vitro measurements

- CFD model validated with spray velocity and deposition data was used to investigate the effects of spray cone angle, spray velocity, plume, ovality, and droplet size distribution
  - Rank order: most influential parameter = spray cone angle > plume ovality > characteristic droplet size > spray velocity > uniformity constant of droplet size distribution

- Research developed adult and pediatric in vitro nasal models to evaluate regional deposition of nasal spray drug products with typical spray device design and CFD model to determine relationships of in vitro metrics of spray properties with regional deposition.

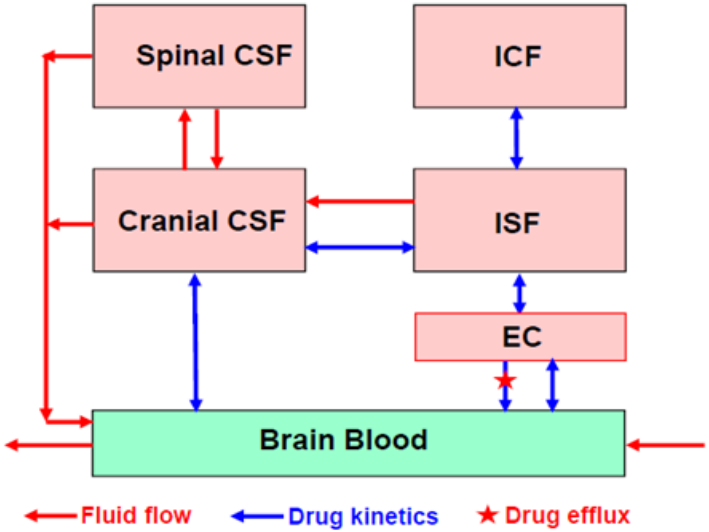
Nose-to-Brain Drug Delivery

Grant U01FD007657 with The University of Manchester (ongoing)

Objective: Development of a physiologically based PK (PBPK) model that will link the nose-to-brain pathway to the disposition of drug within the central nervous system and the rest of the body

- Nose-to-brain PBPK model will be combined with pre-existing five compartment brain PK model
- In vitro permeability, transport kinetics, and novel proteomics data will be collected
- Crossover PK studies will be conducted following intravenous or oral and intranasal delivery of zolmitriptan, naloxone, and oxycodone

- Establishing BE recommendations for potential generic nose-to-brain NDPs is complicated as there are currently no FDA-approved reference listed NDPs with proven olfactory targeting.



A schematic representation of brain PBPK model (CSF= Cerebrospinal Fluid, ICF= Intracellular Fluid, ISF=Interstitial Fluid, EC=Endothelial cells)

Conclusions

- Nasal drug products (NDPs) are becoming increasingly diverse, which creates complexities and challenges for generic development and establishing bioequivalence
- In general, BE recommendations focus on the NDP's site of action (local or systemic) and drug state (solution or suspension).
- Based on GDUFA-funded research, NDPs that previously required comparative clinical endpoint BE studies (locally acting suspension nasal sprays) were revised to include **two BE options**:
  - Option 1 is an **in vitro only** pathway to demonstrate BE for T and RS product formulations that have no difference in inactive ingredients (e.g., can be Q1 and Q2 the same)
  - Option 2 provides a pathway for T and RS products to demonstrate BE via **in vitro and in vivo studies**
- Advances with anatomical nasal in vitro models and in silico modeling techniques have provided new tools with potential for building a better understanding of nasal product performance.
- FDA is continuing to conduct research on nose-to-brain products, considering this is a challenging area of product development, with focus on implications of nose-to-brain delivery for future generic product development.

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