Intranasal Drug Delivery: Drug Development Considerations

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Why the Nose?

- Rapid, fast onset
    - Nasal epithelium highly vascularized
    - Large absorption area
- Non-invasive
    - Painless, no needles or injections
    - Easy administration by patient or caregiver
- Amenable to peptides, oligos and biologics
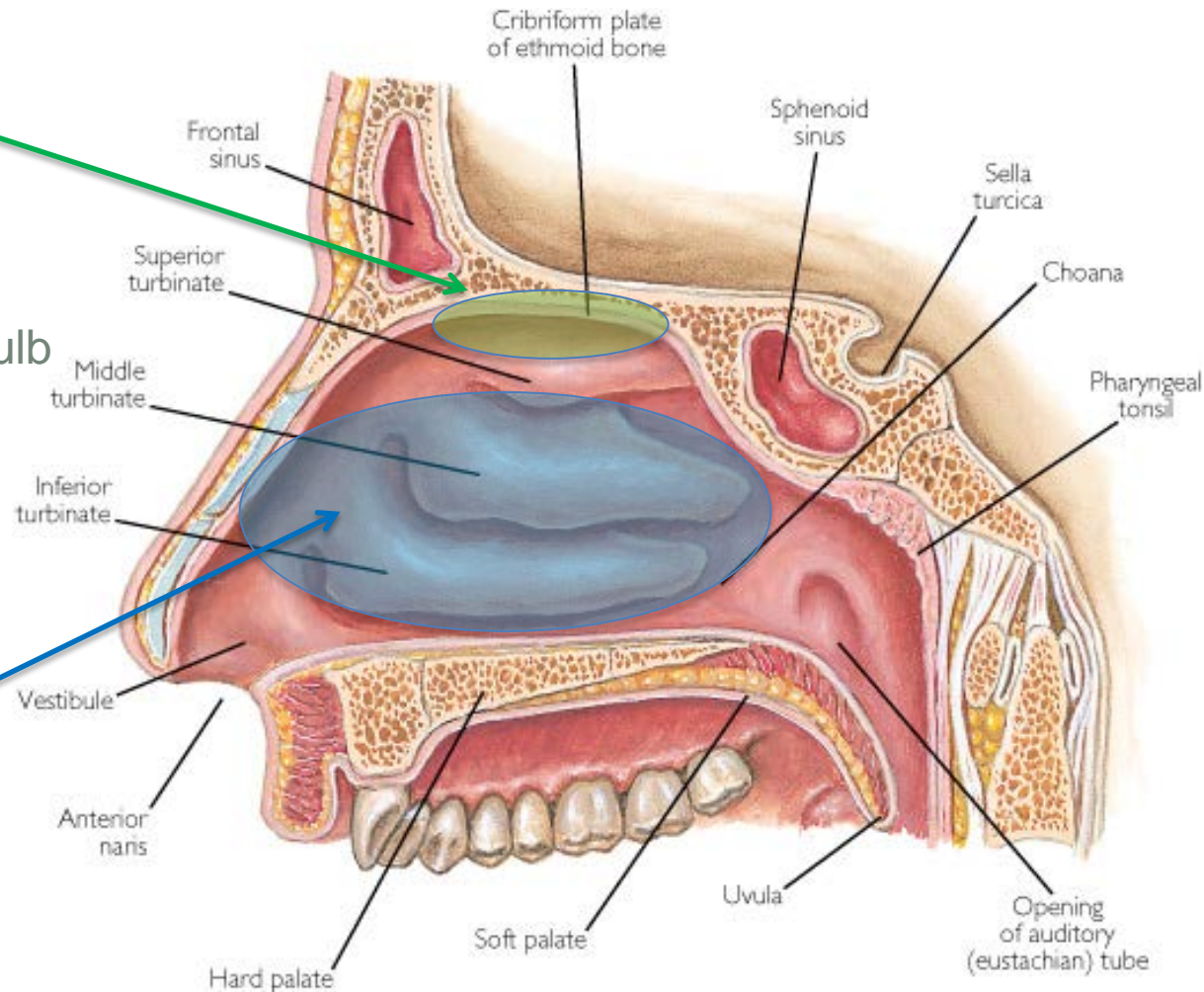   - Avoid gastric degradation
    - No hepatic first-pass metabolism
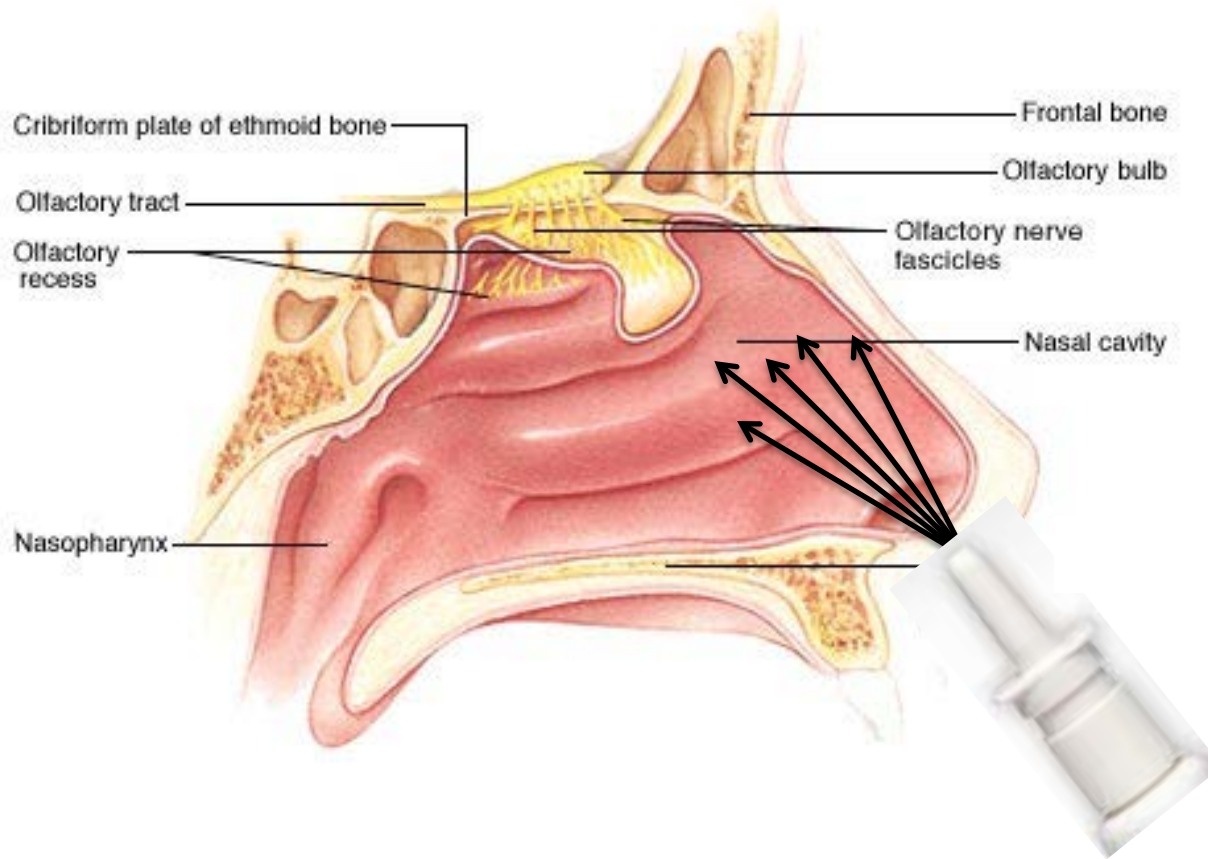
The Nasal Cavity

Olfactory epithelium

- Roof of the nasal cavity, represents ~10% of total surface area
- Direct access to olfactory bulb

Respiratory region

- Epithelial tissue highly vascularized
- Site of drug absorption to systemic circulation

Cribriform plate of ethmoid bone
Sphenoid sinus
Sella turcica
Choana
Frontal sinus
Pharyngeal tonsil
Superior turbinate
Middle turbinate
Inferior turbinate
Vestibule
Anterior naris
Hard palate
Soft palate
Uvula
Opening of auditory (eustachian) tube

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Nasal Drug Delivery

Cribriform plate of ethmoid bone

Olfactory tract

Olfactory recess

Nasopharynx

Frontal bone

Olfactory bulb

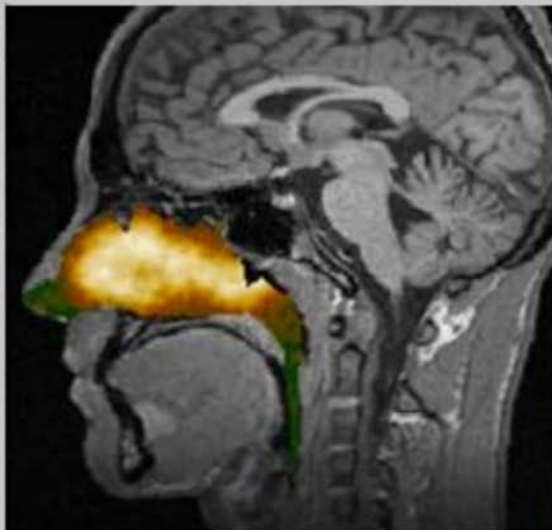Olfactory nerve fascicles

Nasal cavity

From McGraw-Hill

Nasal Spray Distribution

Gamma-scintigraphy images from the same subject
Cumulative distribution during 32 minutes

White areas in the nose = 20% or more of the max intensity
Orange areas indicate = 0-20% of max intensity
Green areas in the nose = No deposition
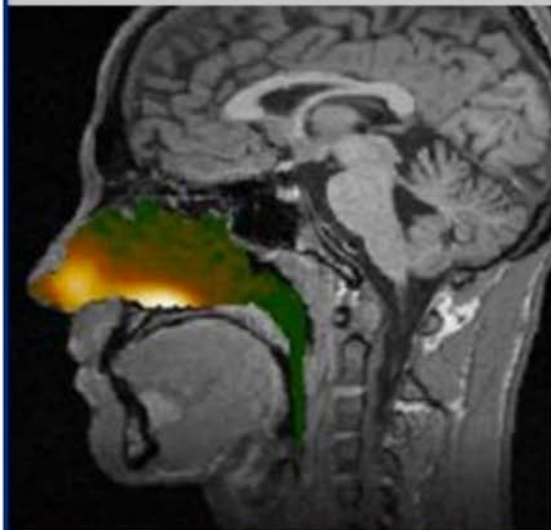
Traditional Spray Pump | OptiNose

Optinose:
Breath-powered delivery

Impel: Pressurized
Olfactory Delivery

Drug Development Considerations

Product Characterization

- Objectives
    - Reproducibility of content
    - Consistency of delivery
- Potential impact on both
    - Safety
    - Efficacy
- Nasal drug products
    - Formulation
    - Spray device

Physical and Chemical Tests

Test Parameter	Description
Description	Appearance, size, color should be tested and within acceptance criteria.
Identification	Two independent chromatographic procedures used to verify the identity of the drug substance in the drug product.
Assay	Analytical determination of drug substance and stability determination.
Impurities and Degradation Products	Levels of impurities and degradation products to be determined by a validated analytical procedure. Impurities > 0.1% must be reported and specified.
Preservatives and Stabilizing Excipients Assay	If present, preservative, antioxidants, chelating agents, or other stabilizers should be assayed.
Microbial Limits	Microbial quality should be controlled and show that the product does not support the growth of microorganisms throughout expiration. Tests should include total aerobic, yeast and mold count, and absence of designated organisms.
Net Content	Net content of the formulation in each container should be within release specifications.
pH	pH should be within acceptance criteria.
Osmolality	Osmolality should be tested for products that contain an agent to control tonicity.
Viscosity	Viscosity should be tested for products that contain an agent contributing to the viscosity, both upon release and during stability.

Adapted from: FDA: Guidance for industry: nasal spray and inhalation solution, suspension, and spray drug products

Nasal Formulations

- Absorption enhancers
  - Surfactants, cyclodextrins, bile salts, tight-junction modifiers
- Osmolarity
  - Iso-osmolarity: ~280 mOsm/kg
  - Hypo-osmotic (<50 mOsm/kg): can improve absorption, but also increase potential for epithelial damage
  - Hyper-osmotic (>900 mOsm/kg): increase in mucus secretions
- pH
  - Nasal cavity is slightly acidic, pH 5.5-6.5
  - pH <3 or >10 has been shown to result in histo damage
  - Irritation can occur outside physiological range
- Viscosity
  - Can increase residence time in nasal cavity, but also affect spray characteristics (droplet size)

Nasal Spray Device Tests

Test Parameter	Description
Pump Delivery	Pump delivery testing should be performed to assess delivery and reproducibility. Typically, the weight of individual sprays should be within 15% or the target weight, and their mean within 10% of the target weight.
Spray Content Uniformity	Individual sprays should be analyzed for drug substance content in multiple sprays, at the beginning and at the end of an individual container, among containers and among different batches.
Spray Pattern and Plume Geometry	Spray pattern testing should be performed on a regular basis, and acceptance criteria should include shape and size of the pattern. Plume geometry is typically established during the characterization of the product and does not need to be tested routinely after.
Droplet Size Distribution	Droplet size distribution should be controlled in terms of ranges for the D_{10}, D_{50}, D_{90}, span and percentage of droplets <10µm.
Particle Size Distribution	Required for suspension nasal sprays only, and should include acceptance criteria for particle size distribution of the drug substance particles in the formulation.
Particulate Matter	Levels of particulate matter should be tested with appropriate acceptance criteria.
Weight Loss (Stability)	Weight loss should be assessed for samples stored on stability, in two different container orientations.
Leachables (Stability)	Analytical methods to identify, monitor and quantify leached components should be established.

Adapted from: FDA: Guidance for industry: nasal spray and inhalation solution, suspension, and spray drug products

Additional Drug Product Characterization

- Pump priming and sprays per unit
  - How many actuations needed until the spray unit delivers the desired dose/volume?
  - How many usable sprays per unit?
- Re-priming and in-use
  - How long can a spray unit sit before it needs to be primed again?
  - Will delivery be sufficient when used as per the clinical protocol?
- Preservative effectiveness
 - Will the preservative prevent microbial contamination with use?

Priming and Usable Spray
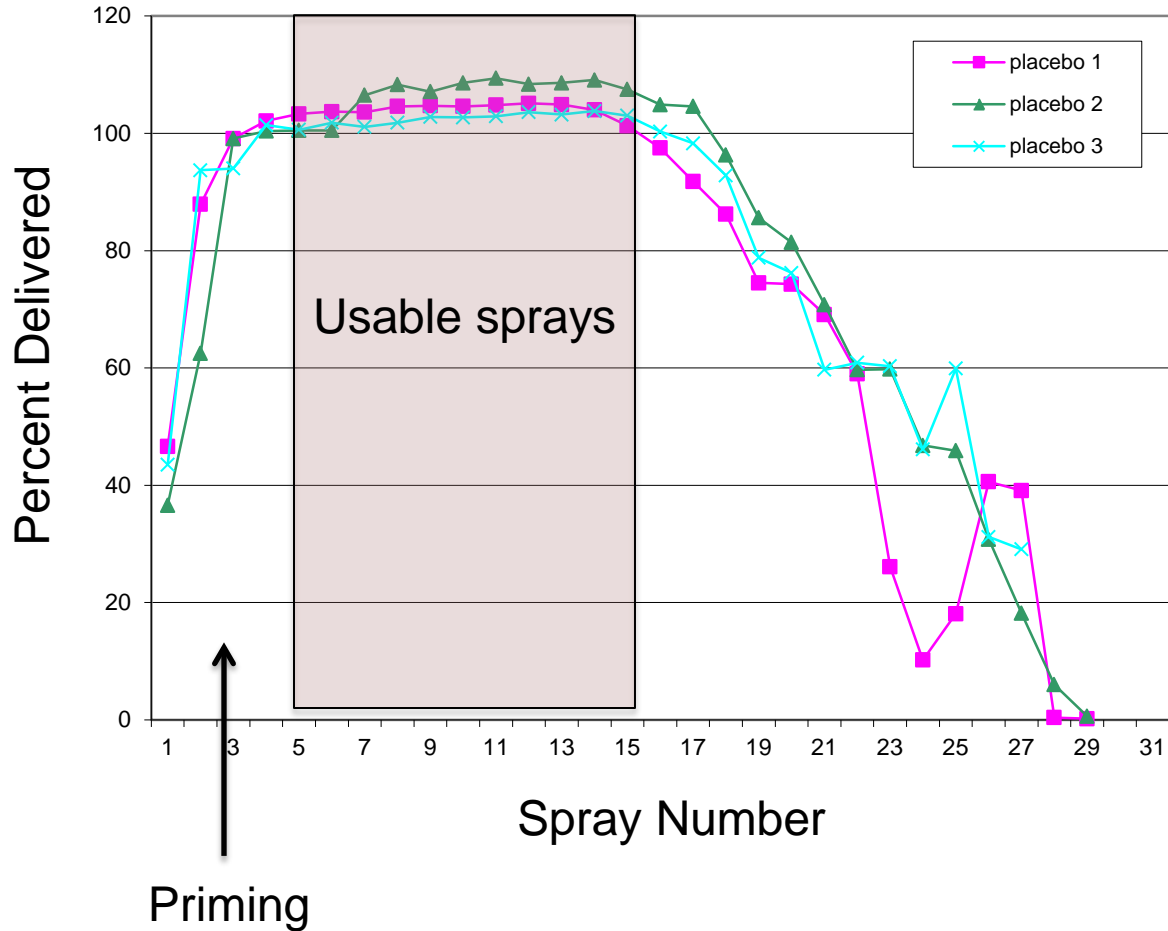
Aptar VP7 pump
3 mL fill

In-use Study

- How long can the spray unit sit before it needs to be re-primed?
  - Spray unit primed then left upright on the benchtop for 4 days
  - Unit then actuated and spray weight measured
- Conclusion: spray units do not need to be reprimed if unused for up to 4 days
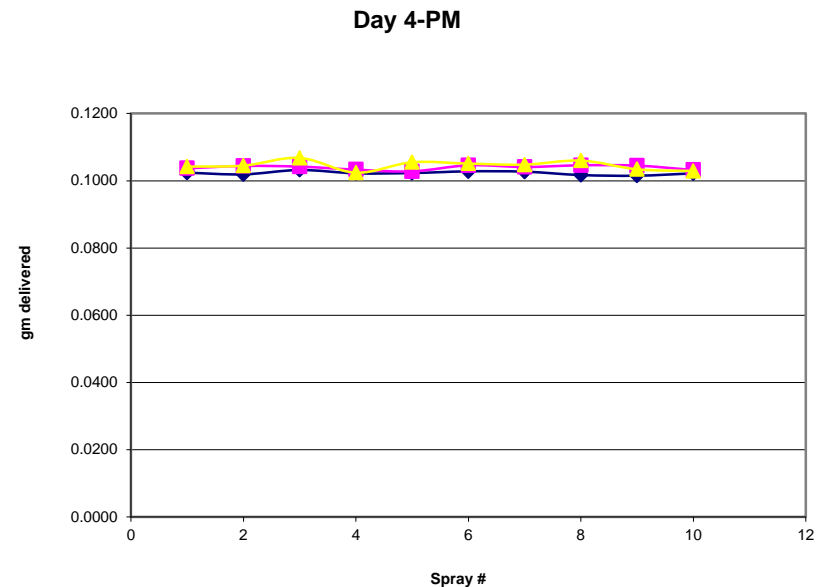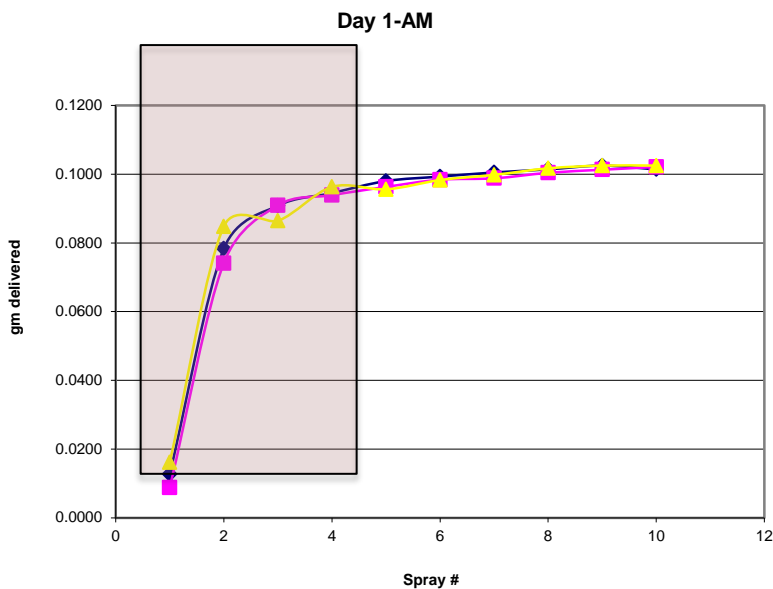
Nonclinical Studies

- Local tolerance – often a function of the formulation (enhancers, preservative)
  - Cultured nasal epithelia
  - Assessment of irritation in tox studies
    - Clinical observations (dryness, secretions, redness)
    - Histopathological evaluation
- Changes in olfactory function
  - Zinc gluconate, case example
  - Histopathology in tox studies
 - Smell identification tests in clinical studies

Nonclinical Studies

- Defining the maximum tolerated dose (MTD)

  - Regulatory agencies want to understand dose and target organ toxicity

  - Multiples of the intended clinical dose not usually sufficient

- Maximum feasible dose (MFD)

  - Justify the high dose tested

  - MFD defined by solubility and volume of administration

    - Volume of administration dependent on species

    - Trade-off: Increasing volume also increases variability

    - Multiple dosing sessions, alternating nares

Comparative Anatomy

http://www.aafp.org/afp/2000/0115/p427.html
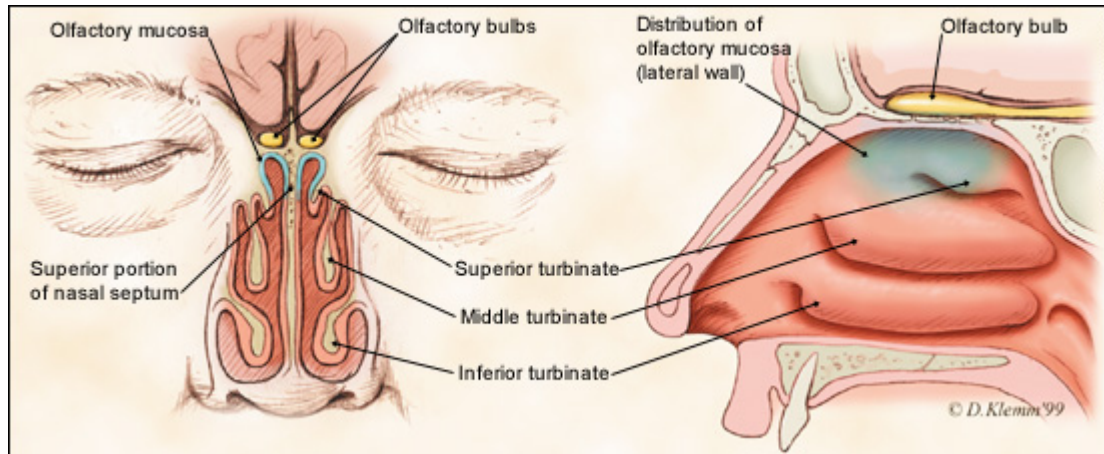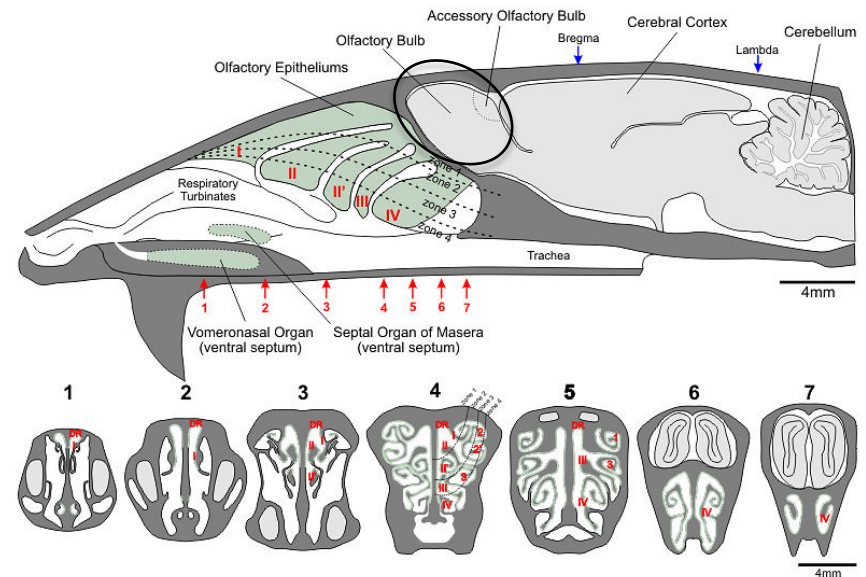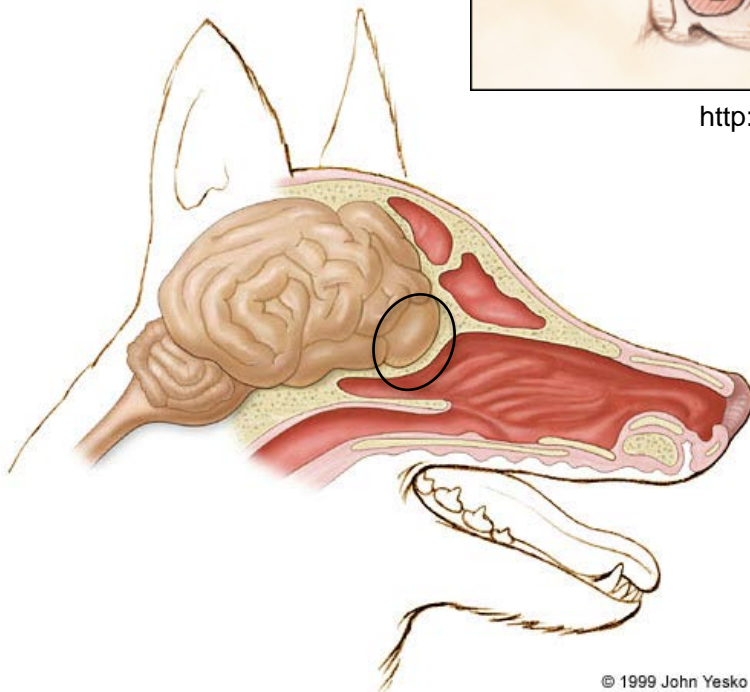
Species Comparison

	Body Weight (kg)	Nasal Volume (mL)	Nasal Surface Area (cm^2)
Man	70	20	160
Monkey	7	8	62
Dog	10	20	221
Rat	0.25	0.4	14
Mouse	0.03	0.03	2.8

Adapted from: Gizurarson S: Animal models for intranasal drug delivery studies. A review article. *Acta Pharm Nord* 2(2), 105-122 (1990)

Nonclinical Intranasal Dose Administration

Points to consider

- Rodents
    - Pipettor
    - Dispense small bead
    - Place near nostril
    - Allow normal inspiration for uptake into nasal cavity
- Dogs
    - Incredibly important to train animals to accept dosing
    - Exclude animals that do not take to dosing

Bridge from Nonclinical to First-in-Human

- No Observed Adverse Effect Level (NOAEL) from animal safety studies used to inform a starting clinical dose

- Allometric scaling is one method to compare doses between species

  - For example, body surface area (rather than body weight) is used to scale systemic drugs

  - Scaling for nasal administered drugs is more challenging because of the large differences in intranasal anatomy. From previous table, the nasal surface area-to-body weight is:

    - Human: 2.3
    - Dog: 22
    - Rat: 56

  - If systemic exposure is the objective for nasal delivery, then allometric scaling by dose-exposure can be justified

Case-Study: Intranasal davunetide

Nose-to-brain?

- If intranasal administration bypasses systemic circulation…
  - How to assess exposure for safety considerations?
  - Will anatomical differences between species effect transport to the brain?
  - What is the impact on translation from animal to human?
- For davunetide clinical development program, demonstrated: nose → systemic circulation → brain
  - Rat pharmacokinetic study: continuous CSF collection
    - CSF exposure proportional to systemic exposure <u>and</u>
    - Independent of route of administration
  - Quantitative whole-body autoradiography: kinetic study
    - Intranasal and intravenous administration
    - Showed brain exposure no greater after intranasal administration (compared to IV) for an equivalent dose
    - No increase in olfactory bulb exposure after intranasal administration

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Human Pharmacokinetics (PK)

- Open-label, single dose, plasma and continuous CSF collection
  - Lumbar (L3-L4) catheterization
  - CSF collected at 0.2 mL/min for 4 hours, 1 mL fractions
  - 6 subjects per group
  - Measured drug levels as well as various AD biomarkers
- Healthy Adult (18-45 years)
  - 50 mg intravenous
  - 300 mg intravenous
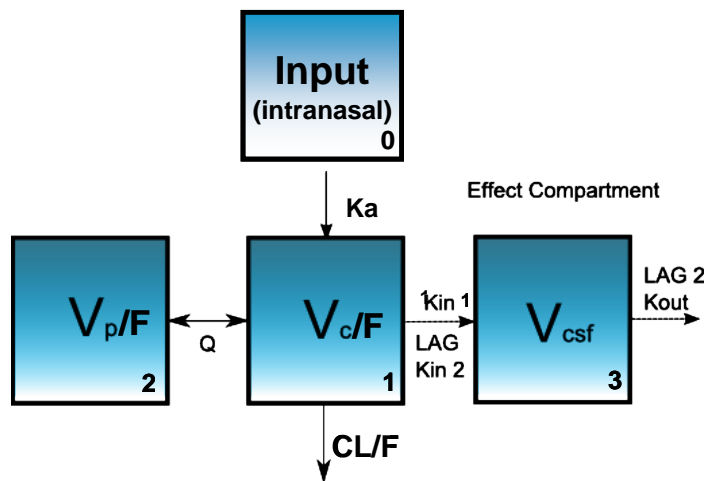 - 15 mg intranasal
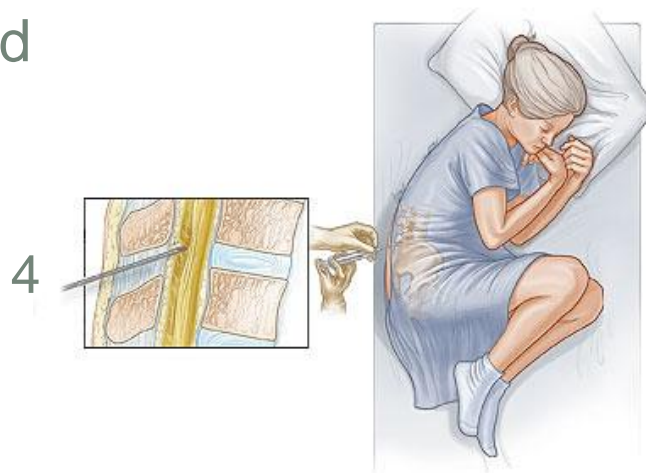
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Plasma & CSF Profile: 50 mg IV

- Continuously collect CSF and plasma
- Healthy subjects (n=6)
- Measure drug levels with validated LC-MS/MS assay
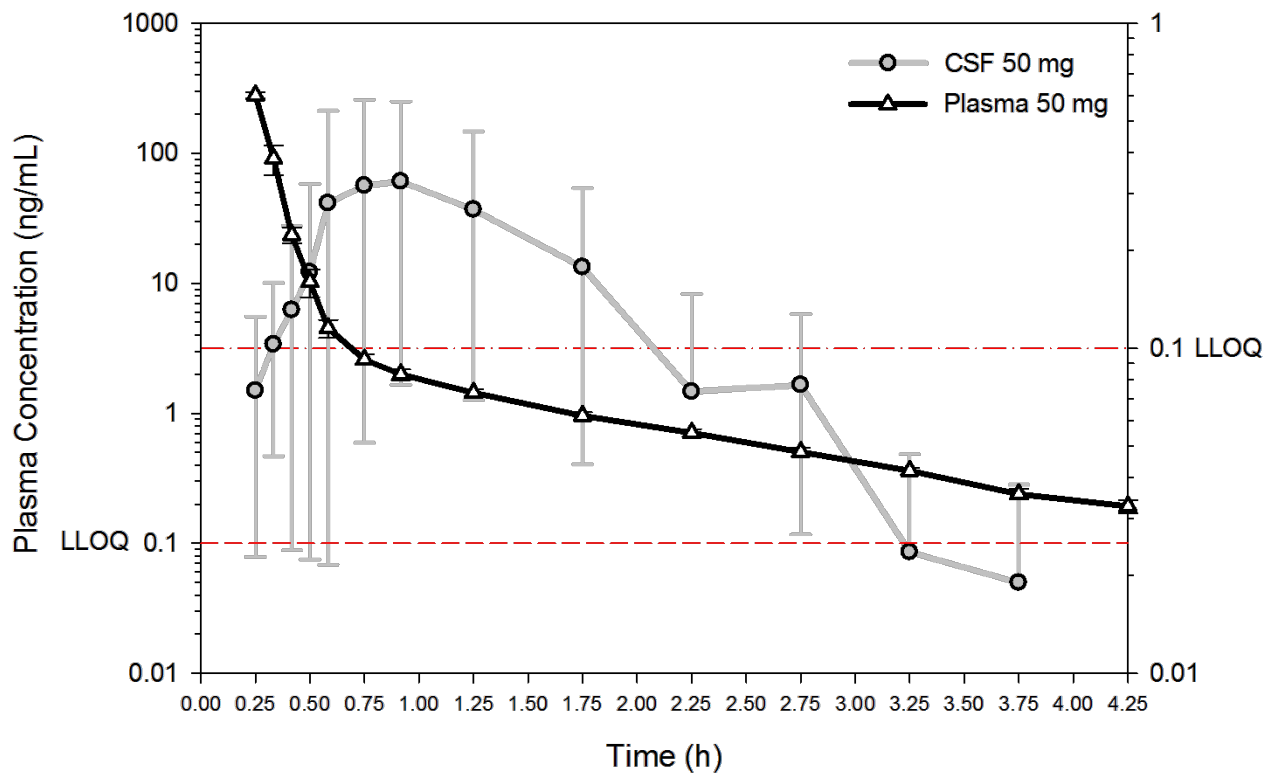
Compartmental PK Modeling

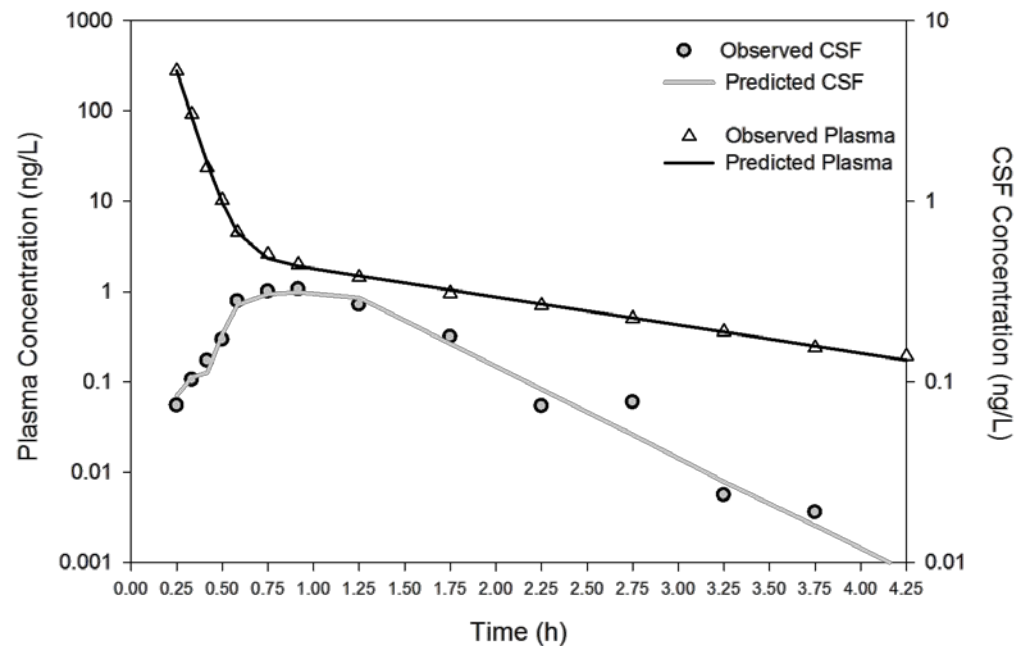- Explored various compartmental PK models
- Best fit: Two-compartment model

Computational model predicts experimental data

Peripheral Volume of Distribution (for IV and IN)

$$\frac{dA_2}{dt} = \frac{Q \times A_1}{V_c} - \frac{Q \times A_2}{V_p}$$

CSF:
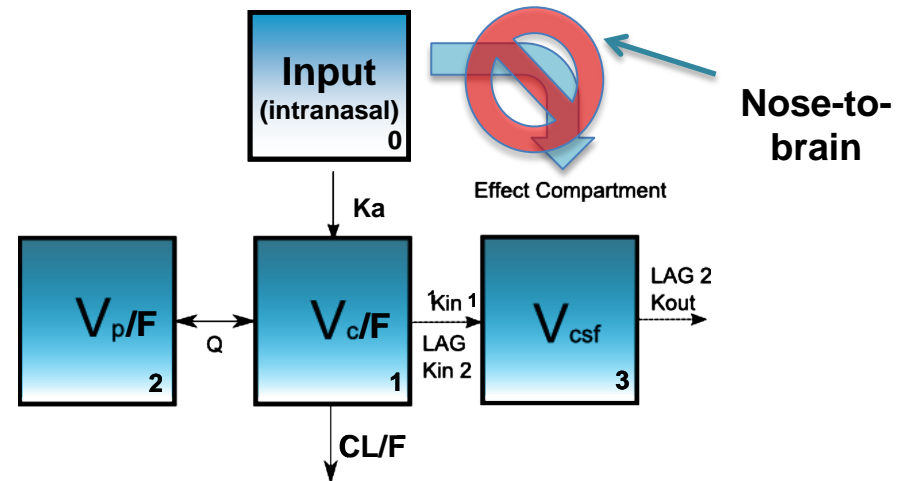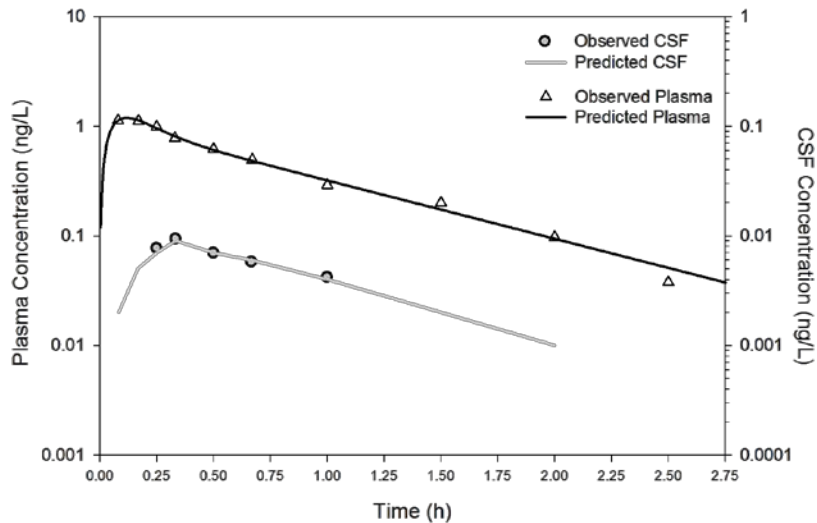
$$\frac{dA_3}{dt} = +\left[\left(Kin1_{0\,to\,LAG1} + Kin2_{LAG1\,to\,LAG2}\right) \times A_1\right] - \left[Kout_{LAG2\,to\,\infty} \times A_3\right]$$

Intranasal PK

- The IV compartmental model fits the intranasal plasma and CSF data

- Suggests pharmacokinetics in CSF is a function of plasma concentrations

- Intranasal drug administration results in systemic distribution (not direct nose-to-brain)

- Compartmental PK model allowed for:

  - PK simulation to evaluate dose and dose paradigms for optimization of steady state CSF concentrations

  - PK model allowed for sparse blood sampling in Phase II/III

Summary

- Advantages

  - Non-invasive

  - Rapid absorption

  - Amenable to peptides and biologics

- Disadvantages

  - More complex drug product characterization and stability

  - Challenges with local irritation, potential for unblinding?

  - Nonclinical dose selection and scaling

  - Potentially low bioavailability

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Questions?

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