NASAL INNOVATION FORUM

IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

Aptar Pharma

Delivering for Patients: Navigating Nasal Routes for Optimal Impact

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September 2025

From formulation to patient.

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Intranasal Market Development Snapshots

1998

First Launch Imigran

Zomig, Instanyl, Narcan (2016)

2018

2020

Valtoco, Tosymra, Spravato, Nayzilam, Baqsimi

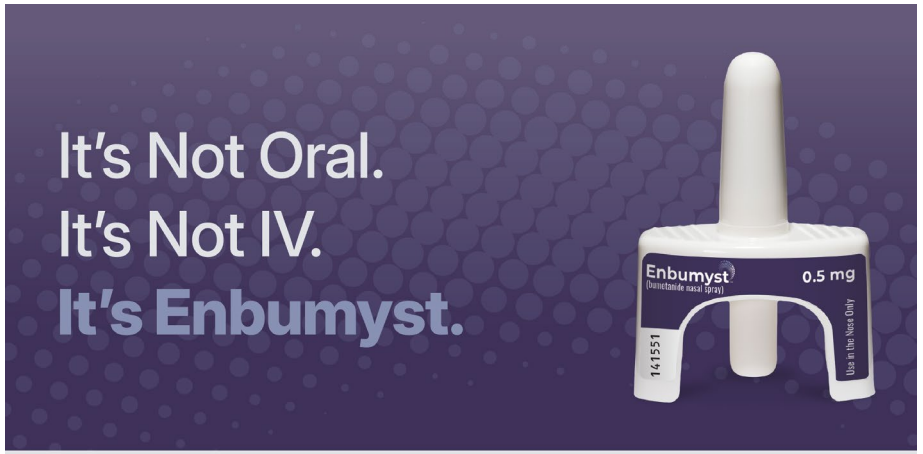
Opvee, Kloxxado, Naloxone, Zavzpret

2023

Relatively IN Products have a faster growth rate. Revenues CAGR for nasal was 29% compared to 2% CAGR for oral & 4% of inj

Total Nasal Rev $2B

Total Injectable Rev $41B



Enbumyst™ (bumetanide nasal spray) 0.5 mg

Benefits of Pre-filled Nasal

Intranasal has rapid onset of action

Administration time reduced

- No mixing or preparation by pharmacist or nurse
- Dosing is less than a minute

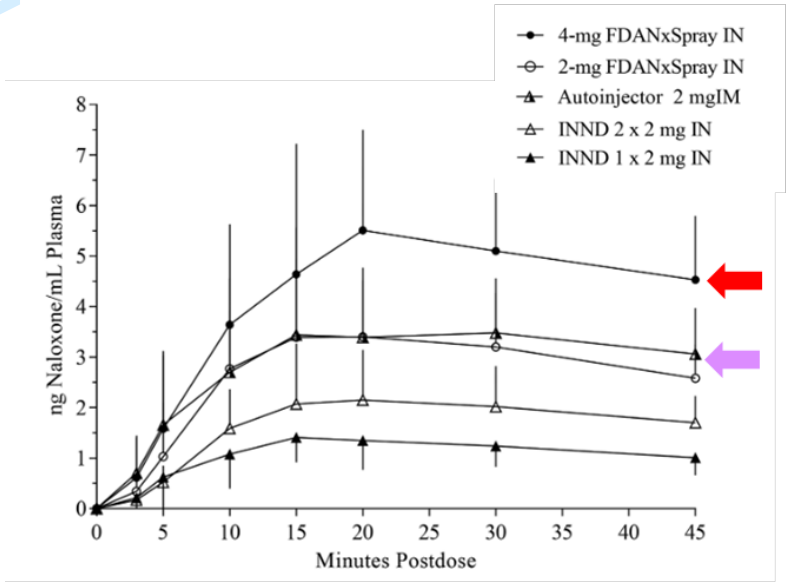
Safe administration by HCP

- No needles and associated waste
- Less chance of dosing errors as nasal spray is prepackaged compared to vials

Intranasal pathways for systemic and direct to CNS can improve effectivity and off-target delivery

Alternative treatment locations

- Satellite clinic instead of hospital infusion center
- Hospital to home



Intranasal (IN) FDA approved dose vs intramuscular naloxone (IM)

Nasal Market Developing Spaces: Pharmacircle New Molecules

Metabolism

- Obesity
- Diabetes

Vaccine &Antiviral

- Covid
- RSV
- Influenza
- Universal Flu
- mabs/ mRNA

Neurological disorders

- Autism Spectrum
- Sleep Disorders
- Prader Willi

Cardiovascular

- Stroke/Heart Failure
- Cardiac Arythmia

Molecules

Neurodegeneration

- Alzheimer's
- Dementia
- Parkinson's
- Huntington
- Multiple Sclerosis

Oncology

- Pain
- Glioblstoma
- Breast Cancer
- Brain cancer
- Meningioma

Mental Health

- Depression
- Addiction
- Bipolar Disorders
- ADHD
- PTSD/Anxiety
- Schizophrenia

Traumatic Injury

- Traumatic Brain Injury
- Newborn Brain damage
- Spinal Cord Injury

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The Intranasal Combination Product Trilogy

Patients

Formulation Optimization

Device Optimization

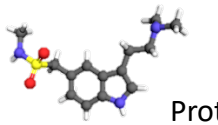
Combination Product

Therapeutic Indication

Nasal Device

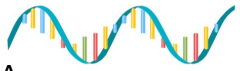
Formulation

Device & Formulation Optimization



Protein

mRNA



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Device Selection Process

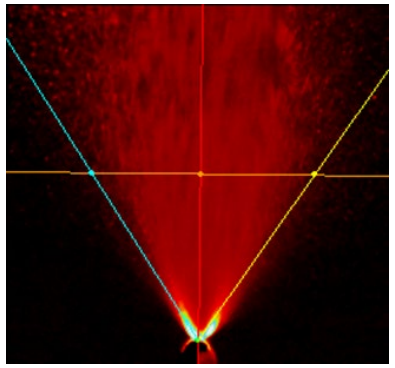
Which device?

- Dosage form (liquid, powder)
- Concentration/Dose volume
- Rheology

Droplet size by Malvern Spraytec

Can I spray it?

- Shear forces
- Droplet size
- Plume characteristics

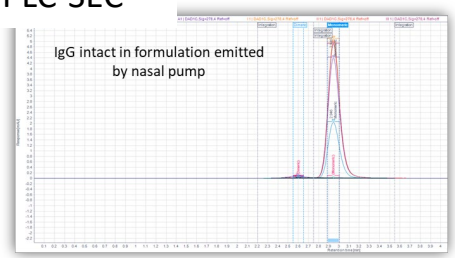


Plume geometry by SprayVIEW (Proveris Scientific)

Compatibility Device Formulation

- Integrity
- Aggregation
- Quantification

HPLC-SEC



Deposition

- Where is the target in the nasal cavity?

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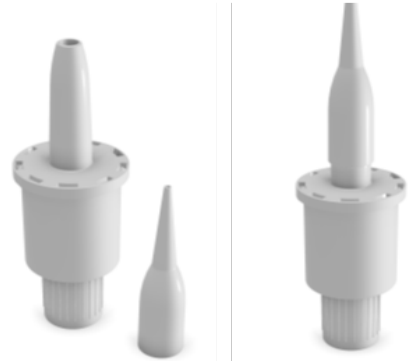
Delivery Solutions for Pre-Clinical Studies

PADA
(lung powder - mice)

Fine Mist Sprayer
(lung/nose liquid – mice)



UDS Powder Pediatric
(nose powder – medium/large animals)

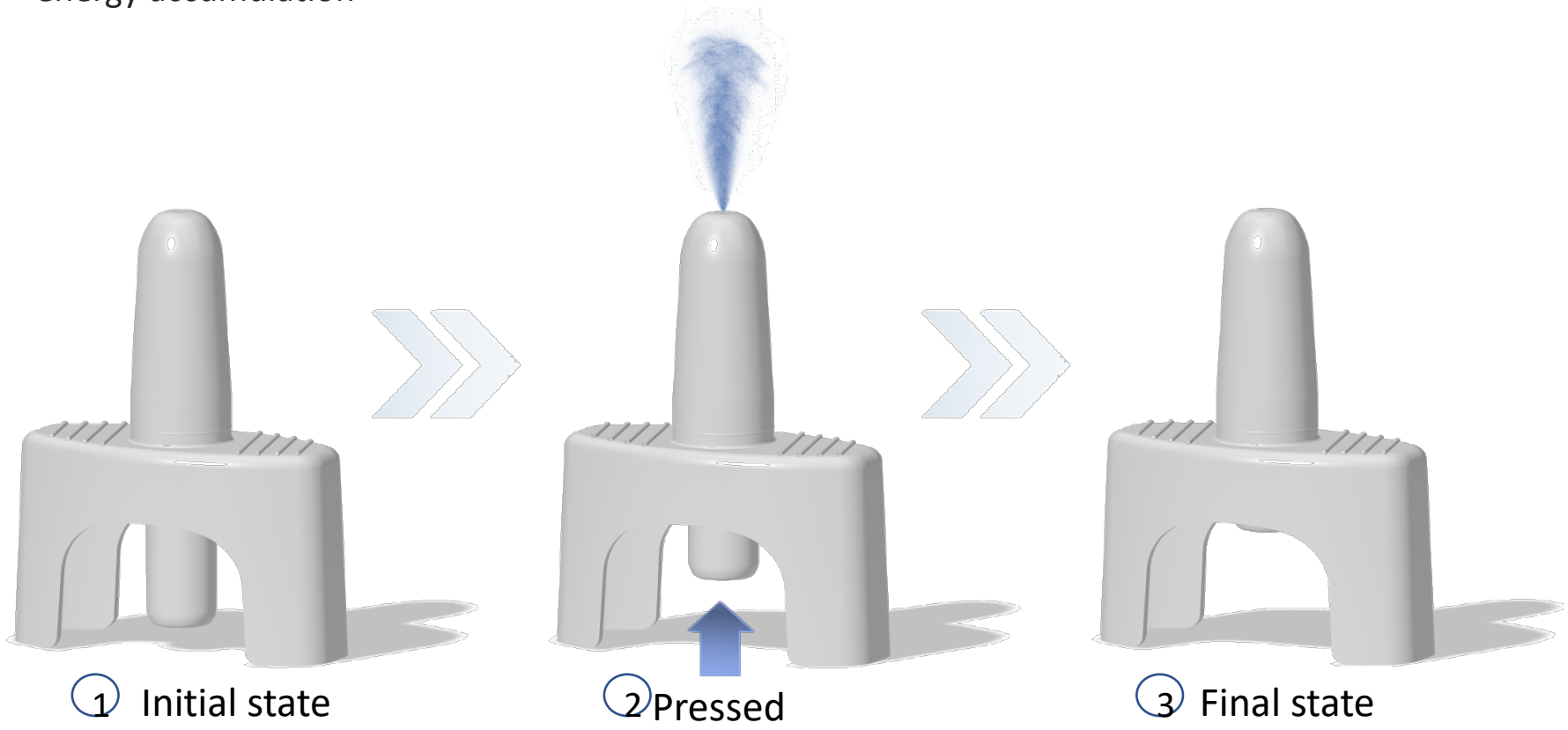
VP7-232NE Pediatric
(nose liquid – medium/large animals - multidose)

UDSL Liquid Pediatric
(nose liquid – medium/large animals)

UDSl Marketed Standard for Intranasal Delivery

- 30 years from first product launch on the market
- Ready to use, primeless device
- Delivery of metered dose
- Dosage of 100 µl with standard filling volume of water
- Reproducible spray performance by user-independent energy accumulation

- Address high reliability target
- One-hand actuation, can be used in any position
- Aptar Plunger cmpatible with UDSl Design
- Small quantity of compatible Vials could be supplied
- Customized design possible



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Actuation Force Case Study

Human factors studies can help understand target patient groups can handle and actuate devices

Help understand how well patients can use devices and satisfy regulatory expectations with regard to HF studies.

Overall results of the manual actuation data captured from the volunteers (n = 49).

	Study Outcome				
Actuation Force (N)	10	26	43	47	50
% who could actuate	100	100	96	88	71
% who found it difficult to actuate	0	0	39	33	20
% men who found it difficult to actuate	0	0	44	32	16
% women who found it difficult to actuate	0	0	33	33	25

Using prototype devices we studies manual actuation of drug delivery system to understand key parameters:

- Volunteers documented difficulties when force was greater than 40N.
- No differences in adults between men and women
- Type of approach can gather useful information on actuation force to understand actuation human factors

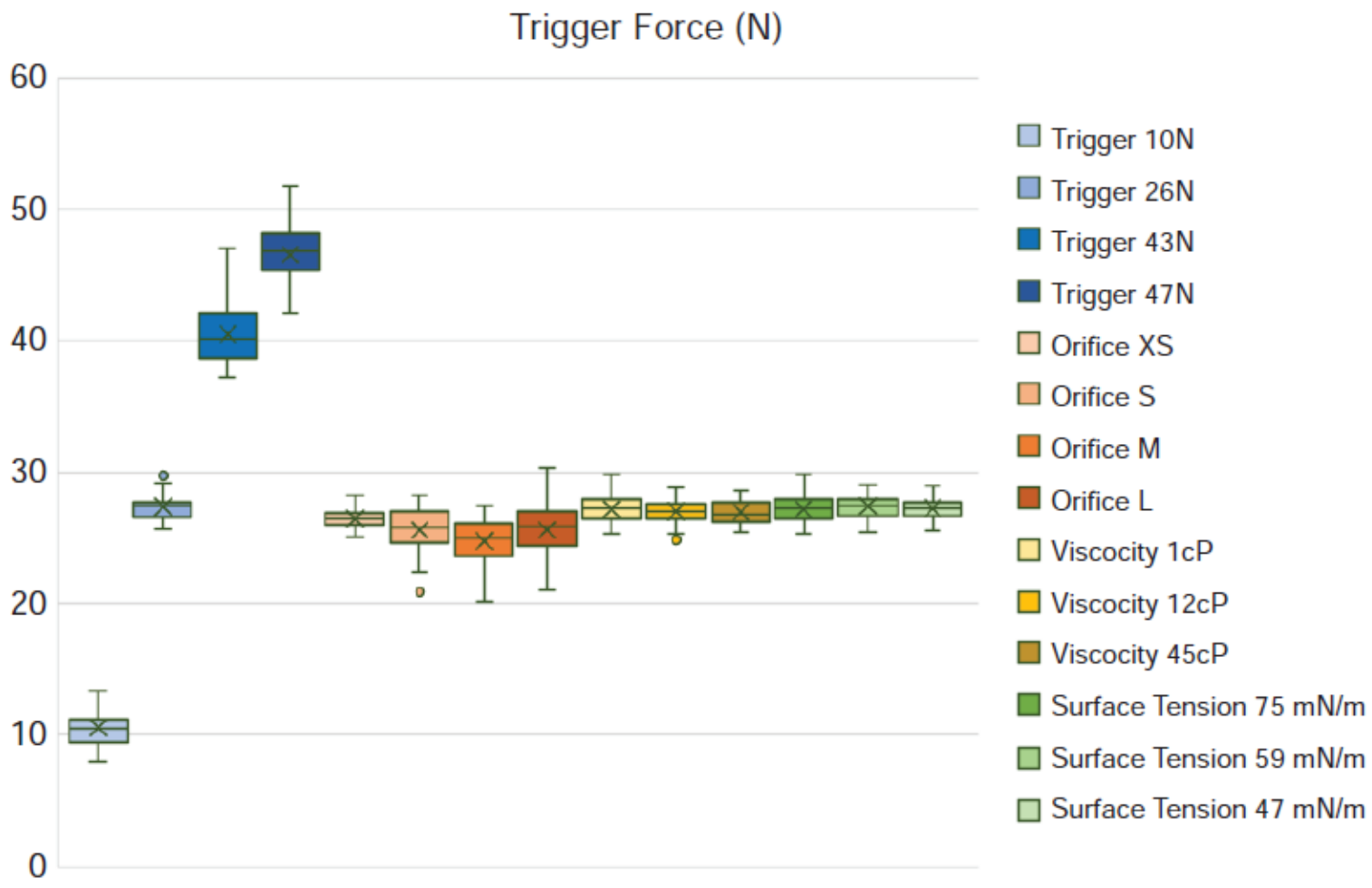
Analysis of Variables Affecting Nasal Spray Product Actuation Force Profile

Surface tension

Formulation viscosity

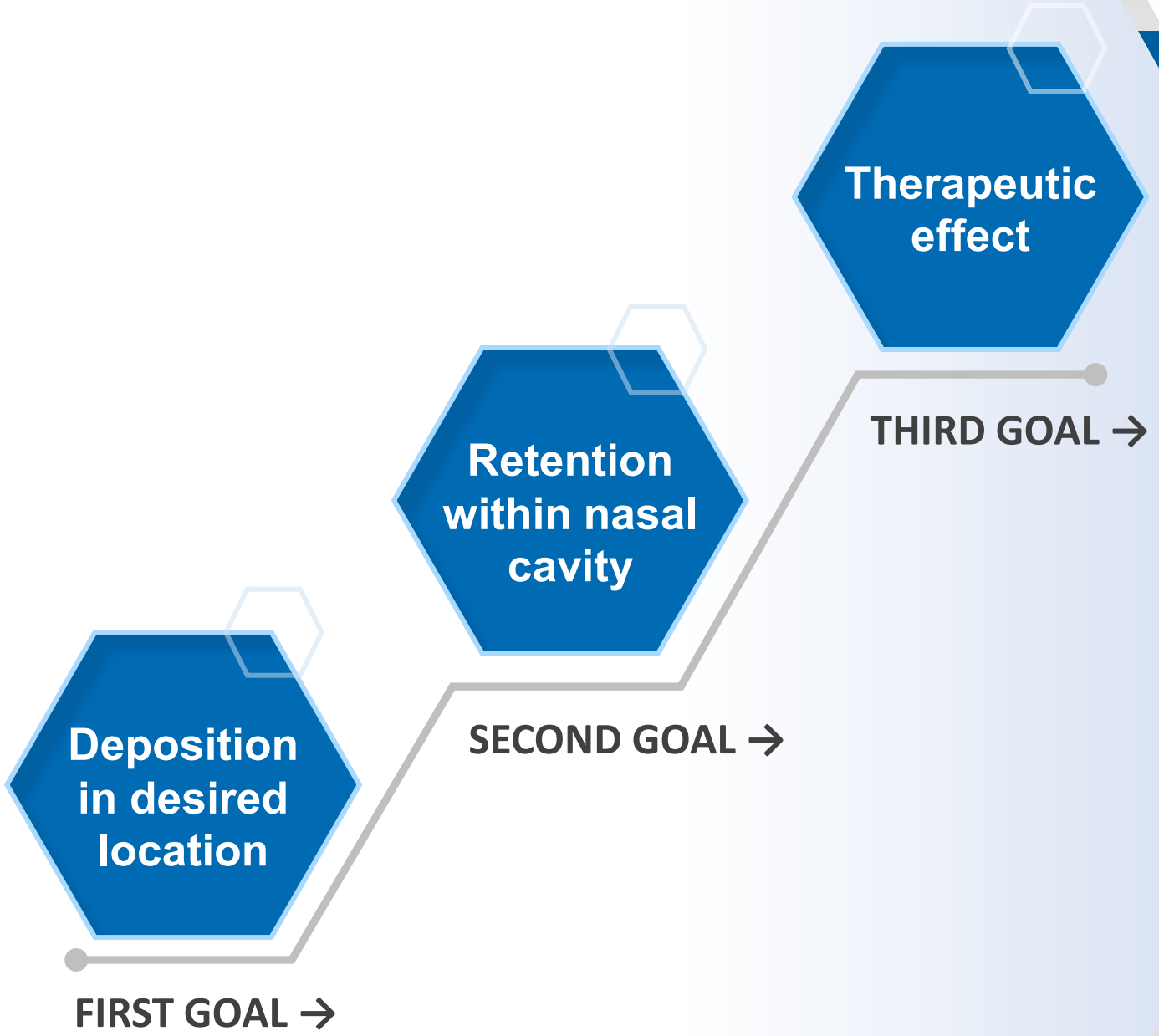
Device orifice

Device trigger force



- Measured trigger force was not impacted by formulation properties or the discharge of liquid through different nozzle orifice diameters.
- Only the mechanical trigger force had a major impact on the maximum force during spray.
- Trigger force is the critical feature to control to ensure users actuate the nasal drug product as intended

Keys to Successful Nasal Drug Delivery



Site of Deposition	• Droplet Size • Particle Size • Droplet Velocity • Anatomy
Mucus Layer	• Lipophilicity • Charge • Molecular Weight
Epithelial Membrane	• Transcellular • Paracellular • Transcytosis
Local Effect or Absorption	• Lipophilicity • Bioavailability
Correct use of device	• Intuitive device • Easy-to-use • Motivation to follow treatment regimen

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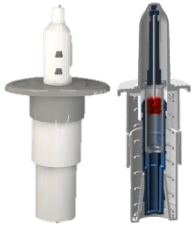
Aptar Nasal Drug Delivery Devices

Liquid Platform

Unidose

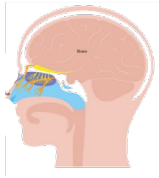
Systemic delivery

UDS Liquid



BDS Liquid

Targeted delivery



Cerespray

Powder Platform

UDS Powder

Aptar CSP protective packaging

Multidose

Systemic delivery

CPS Family Preservative Free

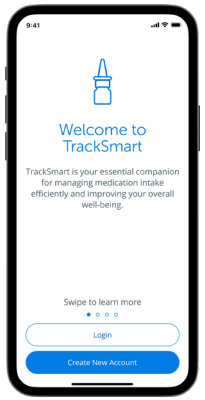
VP7 + CB18

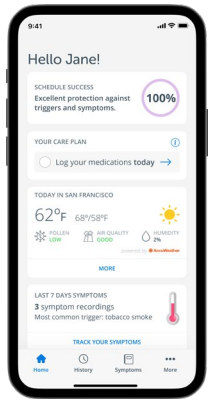
Targeted delivery

Phase I ready

VP7 + N2B Actuator

Connected Platform





An innovative approach to nasal drug delivery, leveraging digital technologies to enhance efficacy and patient experience, starting in early development phases

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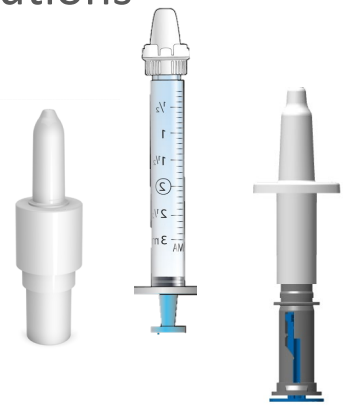
Vaccine Device Strategies & Considerations

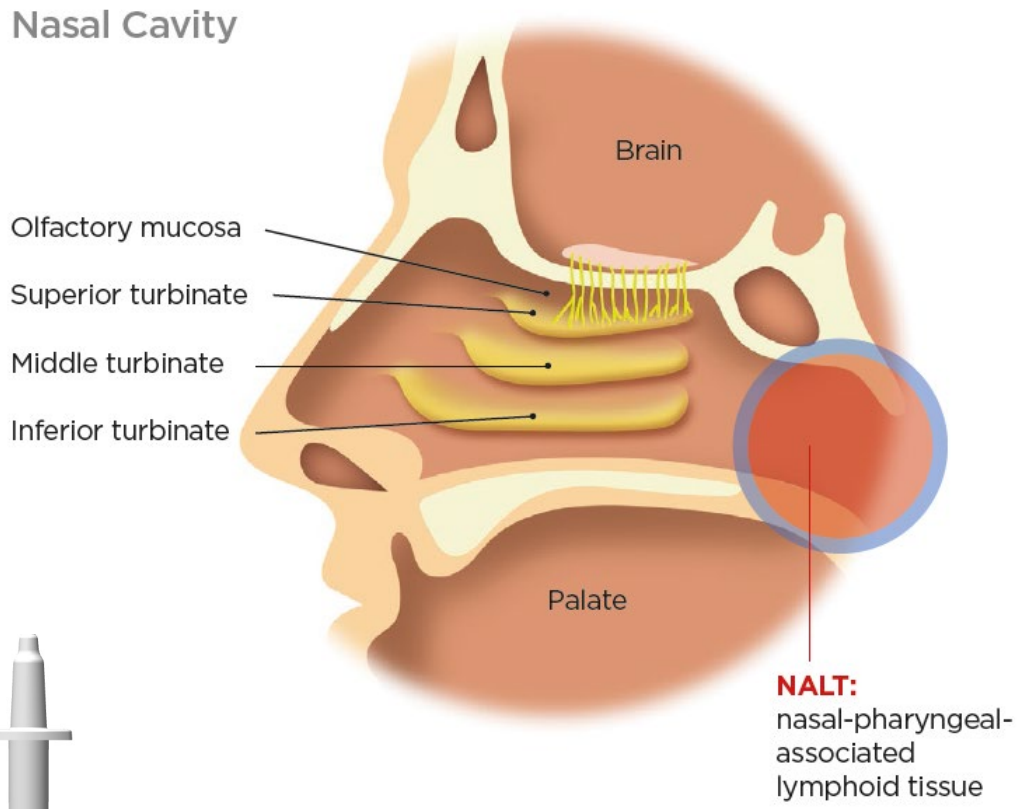
- Vaccines are usually developed as **parental injections**
  - Adaptation of existing products for nasal delivery
  - Use existing manufacturing & supply chain

- Typically contain **biologics**
  - More sensitive formulations
  - Shelf life / storage issues



- Vaccination programmes require **cost-effective** solutions
  - Reusable multi-dose drug products (vials)
  - Preservative free systems
  - Easy to use for HCP outside of clinical setting

- Targeting **NALT region** at back of nose
  - Immunity is generated / immune response triggered



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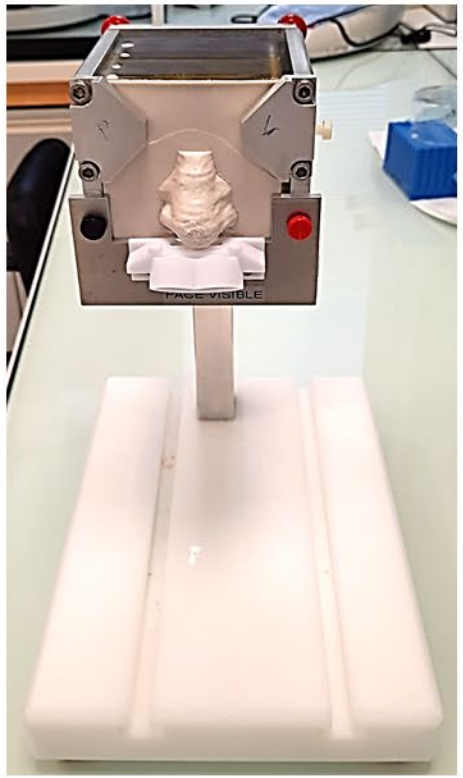
AeroNose™ Nasal Cast to Quantify Deposition

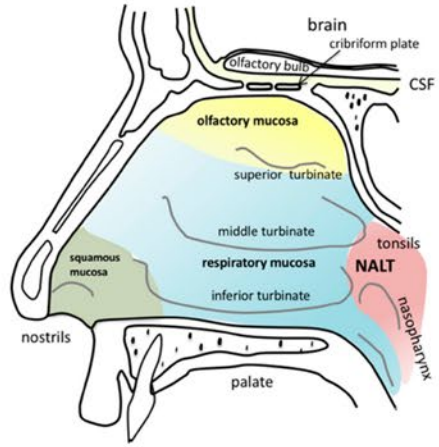
Goal:

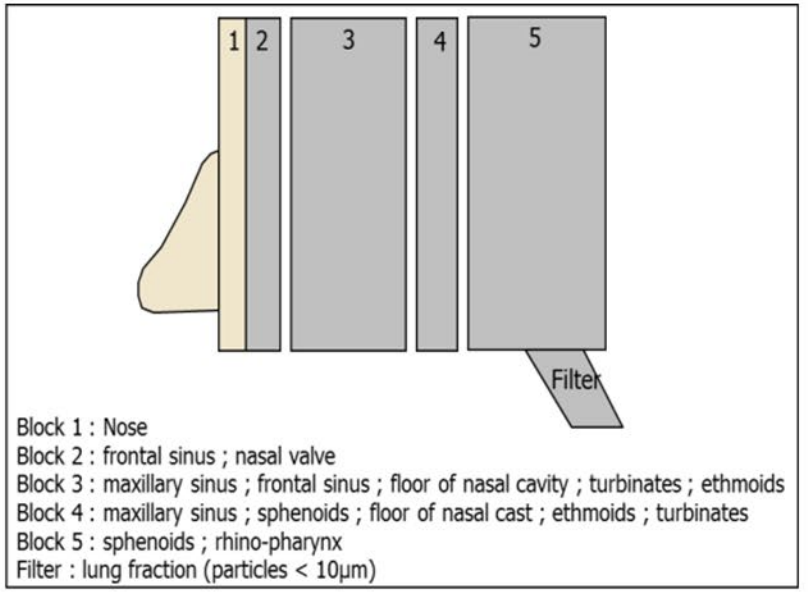
- Determination of % deposition within anterior area

Description of the Nasal Cast :

- 3D representation of the nasal cavity
- Visualization of the spray deposition on each area
- Quantification of the dose on each nasal area







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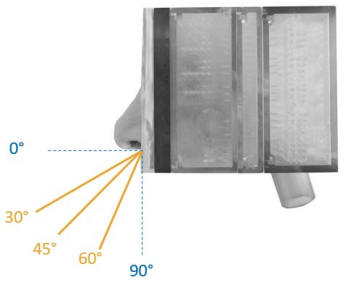
Aptar Pharma Unidose Powder (UDSp)—CNS Applications

- Commercialized device, which has shown consistent deliver to olfactory Ready to use/Primeless
- Active device (patient does not inhale) ensures accurate, consistent dose
- Powder properties influence the spray performance and regional deposition
- Consistent deposition despite changes to orientation



30°	45°	60°	
28%	30%	35%	0°
35%	48%	46%	5°
	26%		10°

% deposition in olfactory region at difference device orientations (10mg)

UDS Powder Disposable

Max. fill volume: 130 mm^3
Fill weight: 10 - 80 mg
Emitted dose weight: >90%

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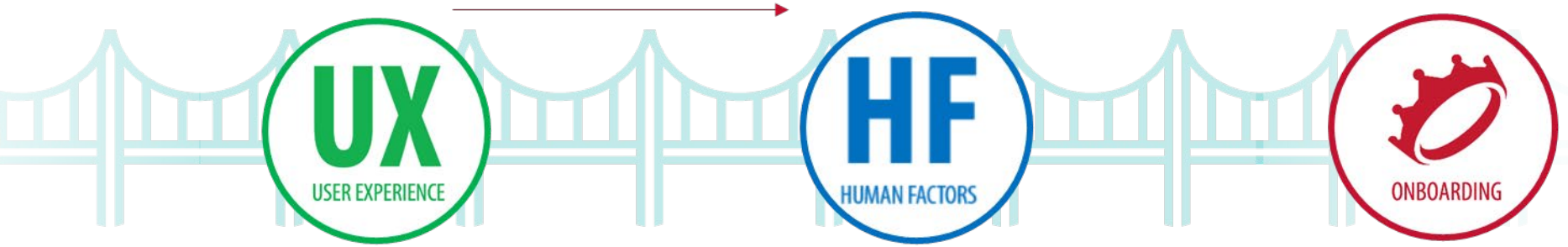
Consider the Patient

Device Selection Studies – An input Formative HF studies, IFU development, Risk Management, etc.



Multidisciplinary approach linking user experience research, human factors regulatory studies and onboarding solutions, accelerating and derisking combination product development for our partners

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Human Factors +

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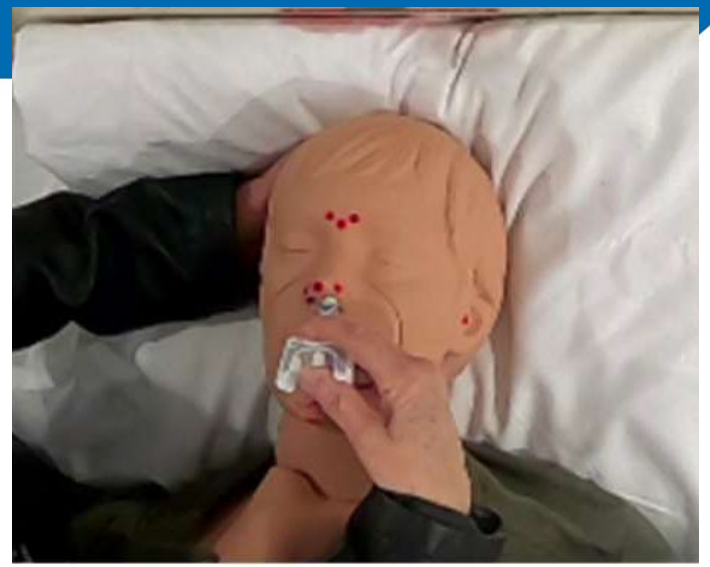
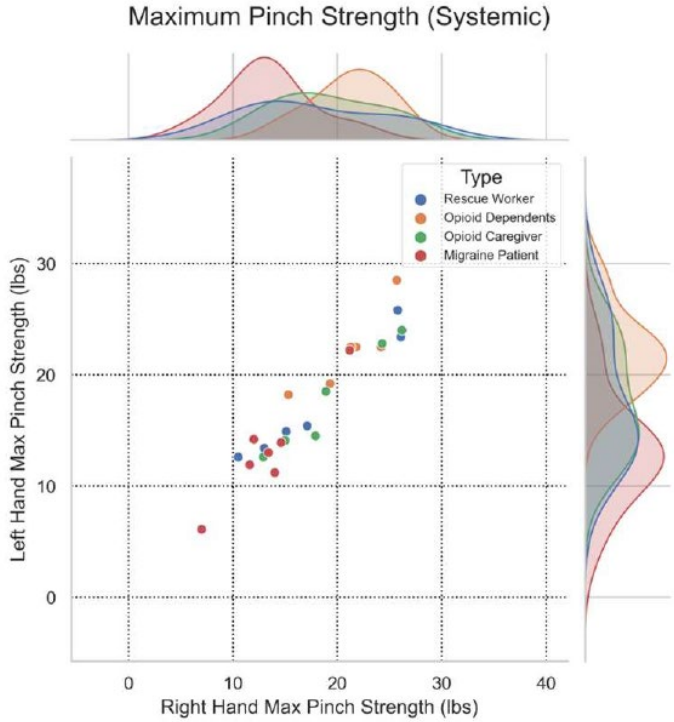
Noble Parkinson & Alzheimer's User Study

- Noble, an Aptar company specializes in offerings to improve patient lives and support the commercial success of brands in the market
  - *Training devices* – Building patient confidence and preparedness through hands on practice
  - *Services* – Developing user centered solutions through user experience, human factors and design
  - *Solutions* – Driving engagement and access to Noble's offerings through channel partners



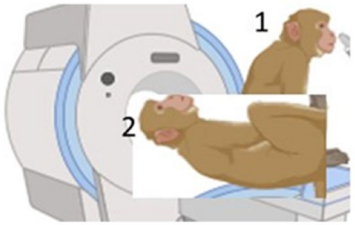
Study Structure

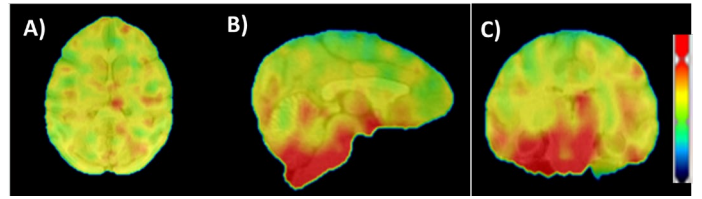
- Introduction
- Patient/Caregiver questions
- Hand size measurement
- Lateral pinch strength measurement
- Product familiarization
- Product simulation for measurements – Patient/Caregiver
- UX feedback for both the products



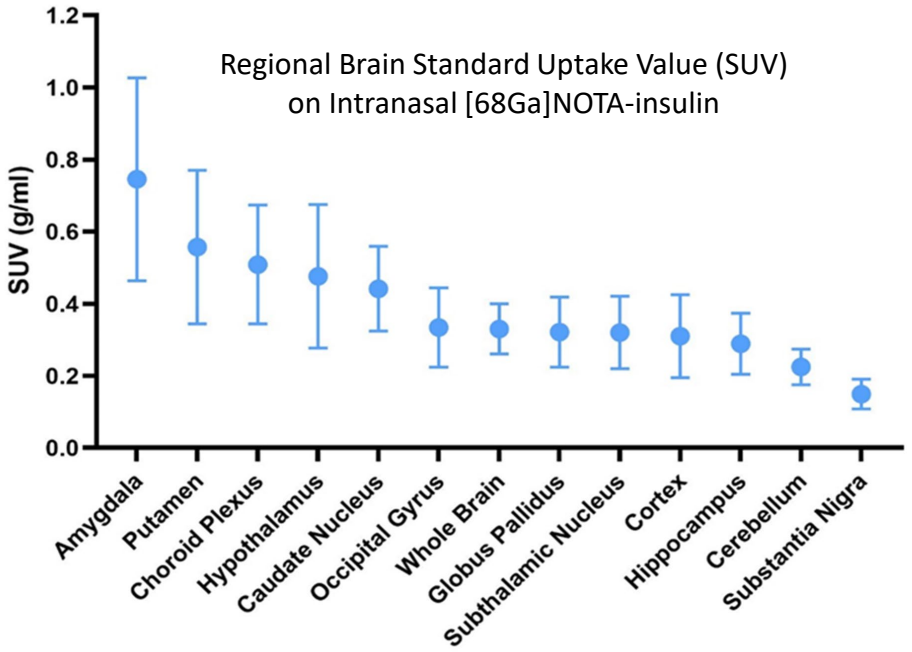
Intranasal [68Ga]NOTA-insulin brain distribution in NHPs

- Dosimetry study in NHPs with [68Ga]NOTA-insulin utilizing an Aptar CPS delivery system to quantify insulin distribution
- Intranasal [68Ga]NOTA-insulin was administered to anesthetized healthy adult vervet monkeys
- Brain regional activity and whole-body dosimetry following PET/CT scans were measured in vervet monkeys
- Aptar CPS successfully delivers [68Ga]NOTA-insulin to the brain
  - Demonstrates regional transport via the olfactory and trigeminal nerves into the brain
- Dosimetry data is favorable for planned future studies of intranasal [68Ga]NOTA-insulin administration in humans





NHP positioning during (1) and after administration (2). Representative a) axial, b) sagittal, and c) coronal brain images after intranasal administration of [68Ga]NOTA-insulin. Red represents highest uptake values.



Solingapuram Sai, Craft et al., First biodistribution study of [68Ga]NOTA-insulin following intranasal administration in adult vervet monkeys, resented at AAIC 24

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Enable the Patient to Start Sooner and Stay Longer on Therapy

Our state-of-the-art products, development services and patient experience expertise enable pharma to accelerate their go-to-market timelines while promoting improved patient outcomes

CLINICAL DEVELOPMENT

Derisk and accelerate development. Enable device based differentiation based on user preferences. Track patient adherence to inc chance of success

REGULATORY

Derisk and accelerate development. Human factors regulation. Over 40 successful HF submissions over the year.

MARKET ACCESS

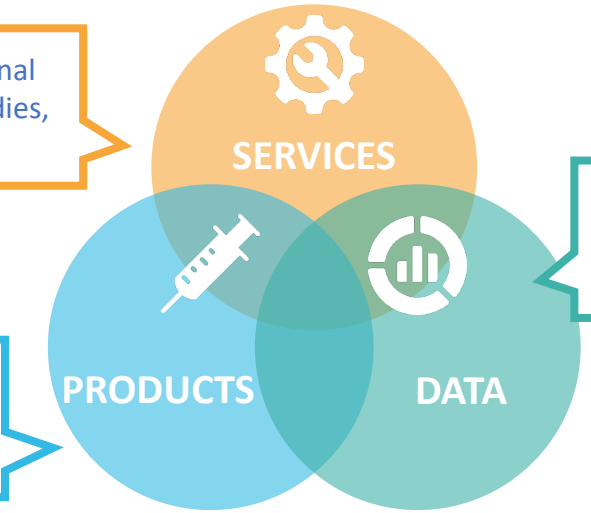
Patient value studies and evidence generations to support marketing HEOR claims.

PRE AND POST COMMERCIALIZATION

Support life cycle management, differentiation and LT adherence. Patient training and engagement to improve speed to treatment and persistence.

COMPREHENSIVE SET OF PRODUCTS, SERVICES AND DATA

Journey mapping, educational material, human factors studies, patient value stories…



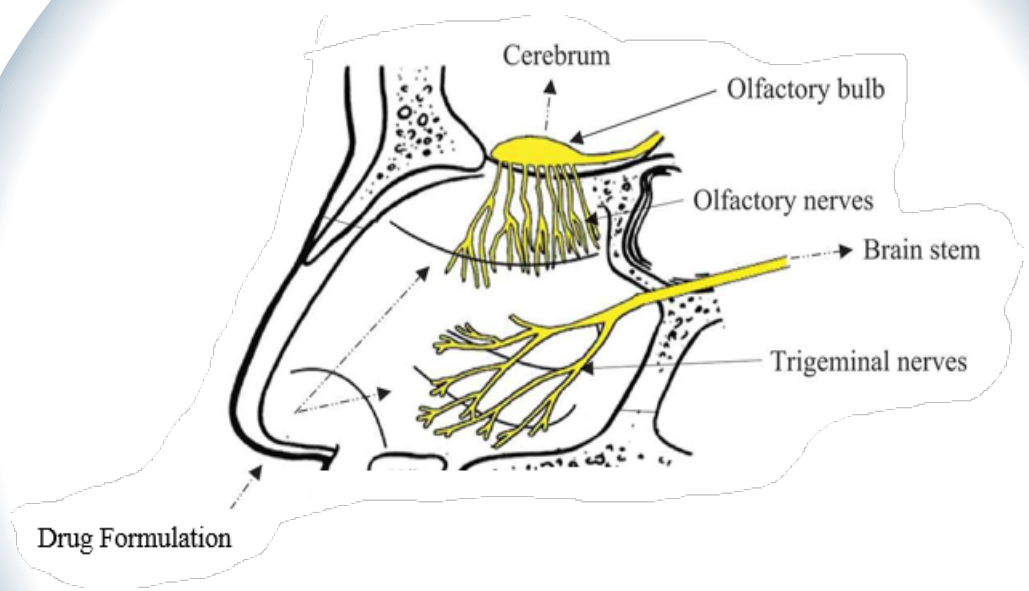
Digitally-enabled solutions, RWD/RWE generation…

Training and onboarding devices

ENHANCED PATIENT EXPERIENCE

- Personalized treatment
- Training to technique
- Medication adherence and monitoring
- Behavioral/lifestyle coaching
- Seamless access and support

Innovating in New Spaces: Nose to Brain direct to the CNS



- Nasal mucosa offers an alternative pathway to the brain that bypasses the BBB -> Targeted delivery to site of action
- Potential to open new therapeutic areas and new molecules to nasal administration
- Highly attractive therapeutic areas fall within the CNS (Central Nervous System) drug delivery arena: Neurodegenerative diseases or Psychiatric conditions ie. Alzheimer's, Parkinson's, depression
- Biologics and complex molecules are showing early promising results with antivirals, mAbs, and peptides. -> Wake Forest Insulin publication

Summary

- Evolution in systemic and CNS drug delivery—opportunity to treat unmet needs
- Evidence of direct nose to brain transport
- Supporting evidence for direct nose to transport in man
- Need to further understand transport mechanisms
- Opportunities for self administration of vaccines
- Incorporate the patient into drug development journey