Post Approval Changes for Nasal Sprays

S Prasad Peri, Ph.D
Eli Lilly and Company
(prasad.peri@lilly.com)

IPAC-RS Nasal Innovattion Forum
Trenton, NJ ***Sept 19, 2025***

Lilly

OUTLINE

- Current Nasal Spray Products
  - Background
  - Indications
  - Components
  - Critical Quality Attributes
  - Regulatory Expectations

- Post-Market Changes
  - Background
  - Nature of Possible Changes
  - Testing Requirements: A Science-Based Opinion

Nasal Product– Products Available

Antihistamine Nasal Sprays:
- Azelastine (Astelin, Astepro)
- Azelastine + Fluticasone (Dymista)

Mast Cell Stabilizer:
- Cromolyn Sodium (Nasalcrom)

Naloxone Nasal Sprays
Product Narcan
- *Strength*: 4 mg/0.1 mL
- *Status*: Over-the-counter (OTC)
- **Kloxxado** – 8 mg/0.1 mL (Rx only; higher dose)
- **RiVive** – 3 mg/0.1 mL (OTC; Harm Reduction Therapeutics)
- **Rezenopy** – 10 mg/0.1 mL (Rx only; approved April 2024)

Neurological Nasal Sprays:
- Esketamine (Spravato)
- Zolmitriptan (Zomig)

Steroid Nasal Sprays:
- Fluticasone Propionate (Flonase)
- Fluticasone Furoate (Flonase Sensimist)
- Budesonide (Rhinocort)
- Beclomethasone Dipropionate (QNasl)
- Ciclesonide (Omnaris, Zetonna)
- Mometasone Furoate (Nasonex)
- Triamcinolone Acetonide (Nasacort)
- Flunisolide (Generic only)

Emergency Nasal Spray:
- Epinephrine (ARS-1)

Other Nasal Sprays (Limited FDA Approval or OTC):
- Xylitol + Iota-Carrageenan (Various OTC brands)

Drug Approvals

Drug Name	Brand Name	Indication	FDA Approval Date
Naloxone HCl	Narcan	Opioid overdose reversal	Nov 2015
Esketamine	Spravato	Treatment-resistant depression	Mar 2019
Fluticasone Propionate	Flonase	Allergic rhinitis	Oct 1994
Azelastine	Astepro	Seasonal allergic rhinitis	Oct 2001
Cromolyn Sodium	Nasalcrom	Allergy prevention	Jul 1983
Epinephrine	Neffy	Anaphylaxis (non-injection)	Aug 2024
Zolmitriptan	Zomig	Acute migraine	Sep 1997
Budesonide	Rhinocort	Allergic rhinitis	Sep 1997
Mometasone Furoate	Nasonex	Nasal allergy symptoms	Oct 1997
Triamcinolone Acetonide	Nasacort	Seasonal allergies	Sep 1996

Global Nasal Spray Market Overview 2024

- **2024 Market Size**:
  - **Global**: $26.2 billion
  - **U.S.**: $10.7 billion (largest share at 44.3%)
  - **EU**: Estimated ~$7.5–8.5 billion (led by Germany and France)
- **Projected Growth**:
  - Global market expected to reach **$49.7 billion by 2034**
  - CAGR: **6.7% globally**, with **U.S. and EU growing steadily**

Product Category	Global Market Share	Notes
Steroid Nasal Sprays	$8.3 billion	Most dominant category
Antihistamine Sprays	~$4.5 billion	Seasonal allergy treatments
Decongestant Sprays	~$3.2 billion	Short-term relief
Combination Sprays	Fastest-growing	12% CAGR through 2030
Emergency Sprays (e.g., Narcan)	~$1.1 billion	Driven by OTC expansion

Nasal Product– Quality Attributes

Characteristic	Description FDA/EMA
Droplet Size Distribution (DSD)	Measures particle size to ensure proper deposition in nasal cavity
Spray Pattern (SP)	Assesses the shape and spread of the spray plume
Plume Geometry (PG)	Evaluates the angle and density of the spray plume
Shot Weight / Delivered Dose	Ensures consistent dose per actuation
Priming & Repriming Studies	Determines how many actuations are needed before consistent dosing resumes
Number of Actuations per Container	Confirms total usable doses per unit
Net Fill Content	Verifies the total volume of formulation in the container
Minimum Fill Justification	Ensures minimum volume is sufficient for dosing and performance
Extractables & Leachables	Assesses potential contaminants from packaging materials
Viscosity, Surface Tension, Osmolality	Physical properties affecting spray behavior and absorption
pH and Buffer Capacity	Critical for stability and mucosal compatibility
Preservative Content & Related Substances	Ensures safety and efficacy of multi-dose products

Device-Dependent Parameters (Valve)

- **Actuation Force (AF)**
- **Stroke Length (SL)**
- **Actuation Velocity (AV)**
- **Return Force (RF)**
- **Return Velocity (RV)**

These influence spray consistency, droplet size, and dose delivery

The following in vitro bioequivalence tests are recommended (FDA):

1. **Single actuation content (SAC)**
2. **Droplet size distribution by laser diffraction**
3. **Drug in small particles/droplets**
4. **Spray pattern**
5. **Plume geometry**

Impact to Critical Quality Attributes*

CONSTITUENTS	COMPONENT	PROCESS/INGREDIENT/PROPERTY	CHANGE
Formulation	Drug Substance	Assay, Particle Engineering/PSD	Yes
		Morphic Form	Yes/No
		Residual Substances/Impurities	Yes
		Surface Properties	Yes/No
	Inactive(s)	Drug Compatibility	Yes
		Vapor pressure	Yes
		Material Compatibility	Yes
		Flammability	Yes
		Co-solvents	Yes
		Preservatives	Yes
Device/CCS	Valve	Volume	Yes/No
		Design	Yes
		Elastomer	Yes
		Leachables	Yes
		Priming	Yes/No
	Actuator	Nozzle Diameter	Yes/No
		Jet Length	Yes/No
		Mouthpiece Shape and Length	Yes/No
		Container	Yes/No

Post-Market Changes

Post-market Changes (Background)
(US FDA Precedents)

Guidance Document	Recommendations Format
Immediate Release Solid Oral Dosage Forms Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation (1995)	Testing & Filing Requirements for Change Levels 1, 2 and 3 in: A. Component and Composition (Excipients) B. Site C. Batch Size D. Manufacturing Equipment E. Manufacturing Process
SUPAC-MR.: Modified Release Solid Oral Dosage Forms. Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Dissolution Testing and In Vivo Bioequivalence Documentation (1997)	
Nonsterile Semisolid Dosage Forms: Scale-Up and Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro Release Testing and In Vivo Bioequivalence Documentation (1997)	
Changes to an Approved Application for Specified Biotechnology and Specified Synthetic Biological Products (1997)	Ranks Changes in terms of potential to have an adverse effect on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product: 1. Substantial, (2) Moderate and (3) Mammal

Post-market Changes (Background)
(The US FDA Precedents – SUPAC-MR)

CHANAGE			TEST DOCUMENTATION	FILING
Category	**Change Levels**	**Example(s)**		
Components and Composition (NONRELEASE CONTROLLING EXCIPIENT)	**Level 1**: Changes are those that are unlikely to have any detectable impact on formulation quality and performance.	Deletion/partial deletion of color/flavor Change in printing Ink	**A.** CMC Application/Compendial Release **B.** Stability testing: one batch on long-term stability data reported in annual report. **C.** Dissolution Documentation (application/compendial)	**Annual report All** information including long-term stability data
	Level 2: Changes are those that could have a significant impact on formulation quality and performance	Change in the technical grade and/or specifications of a nonrelease controlling excipient. Changes in nonrelease controlling excipients, expressed as % (w/w) of total formulation, less than or equal to ranges specified in the Guidance	**A.** Application/compendial product release requirements and updated executed batch records. **B.** Stability testing: 1 batch with 3 months accelerated stability data in supplement, a 1 batch on long term stability data. **C.** Different dissolution testing for extended and delayed release products **D.** In Vivo BE Testing, if dissolution test fails	**PAS: All** information including accelerated stability data **Annual report:** Long-term stability data
	Level 3: Changes are those that are likely to have a significant impact on formulation quality and performance	Changes in the nonrelease controlling excipient range beyond those mentioned for Level 2.	**A.** Same as Level 2. **B.** Stability Testing: One batch with 3 months' accelerated stability data reported in prior approval supplement and long-term stability data of first three production batches reported in annual report. **C.** Different dissolution testing for extended and delayed release products **D**. Single Dose BE study (*May be waived - established IVIVC*)	**PAS:** All information including accelerated stability data **Annual Report:** Long-term Stability data

Testing Recommendations to Support Post-market Changes

- **An Opinion Based on Deliberation Upon the:**
  - Agency Precedents
  - Relevant CQA
  - Advances in Product Development and Testing:
    - Quality-By-Design: Established Design Space(s)
    - Enhance Analytical Method Testing
    - Clinically relevant In vitro Drug Delivery
    - IVIVC
    - In Vitro Dissolution (DS as well Aerosolized Formulations)
    - iBCS
    - Nasal Deposition Based on In Vitro Testing
    - Nasal Deposition In Vivo (Studies)

Regulatory Considerations of Post-market Changes (Nasal Sprays)

COMPONENT	CHANGE		Example(s)	TESTING[2]	FILING[2]
	Level	Description			
Drug Substance	1	Change (s) within the limits established during PD[1], thus unlikely to have detectable effect on formulation quality and performance	Minor shift in micronization parameters	CMC Application/Compendial Release	Annual Report to include stability data
	2	Changes beyond the established limits and/or likely to influence products	Changes in micronization parameters and conditioning, Shift in PSD	**A.** Same as Level 1. **B.** Stability Testing (3 Months). SCU & PSD	**PAS.** Accelerated Stability data Annual Report: Include long term stability data
	3	Changes in established material and process that would affect formulation quality and performance	Change in manufacturing method, sources of starting material, precipitation	**A.** Same as level 2. **B**. Residual substances **C**. Surface Properties, Crystallinity **E.** In Vivo PK Study, if in vitro BE fails, or Realistic In Vitro Testing **D**. Dissolution Testing (If applicable)	**PAS.** Accelerated Stability data , Related substances, In Vitro Testing Data **Annual Report:** Include long term stability data

1. Regulatory Compliant Product Development Including Use of Adequately Validated Methods Using Applicable Current GLP and cGPM

2. With Appropriateness and Adequacy by Seeking Timely Advice From the Relevant Regulatory Agency

Regulatory Considerations of Post-market Changes (Nasal Sprays)

COMPONENT	CHANGE		Example(s)	TESTING[2]	FILING[2]
	Level	Description			
Inactives (Solution vs Suspension)	2/3	Changes/deletion/addition of components, suppliers, release specs supplier or release specs: to be examined case by case.			
Valve	1	Depends on change impacting formulation/device etc.			
	2	Changes likely to affect product performance	Change in the gasket elastomer(s)	**A.** CMC and Compendial Testing, **B.** E&L, SCU, PSD	**PAS:** All information including E&L and Accelerated Stability **Annual Report**: Long Term Stability data to include Leachables
	3	Changes that are likely to have significant impact on product performance	Change in gasket material/design, Change in Valve design	**A.** CMC and Compendial Testing **B.** E&L, Shot Weight, SCU, PSD **C.** In Vitro BE D. In Vivo PK study, if in vitro BE fails	**PAS:** All information including E&L and Accelerated Stability **Annual Report:** Long Term Stability data to include Leachables
Container/label/ Actuation Mechanism	3	If a change is introduced, it might be considered as Level 2/3 change			

1. Regulatory Compliant Product Development Including Use of Adequately Validated Methods Using Applicable Current GLP and cGPM

2. With Appropriateness and Adequacy by Seeking Timely Advice From the Relevant Regulatory Agency

Conclusions

- Post Approval changes in Nasal Sprays are more common that thought
- Time should be spent on preliminary assessments prior to execution of the change
- Post Approval Change management Plan per ICH Q12 should be evaluated for related changes to the extent applicable
- In vitro comparison should always be a starting point for change

Acknowledgements

Dr Gur Jai Pal Singh