Regulatory Topics in Nasal Product Development: Pediatrics and Reliability Expectations

Adam Gibbons[1], Lynn Gold[2], Sana Hosseini[3], Lynn M. Jordan[4], Svetlana Lyapustina[5], Paddy Mccarry[6], Jasmine N. Perriolat[7], Lucas Silva[8], Raphael D. Vincey[9], David M. Wilcox [10]

1 - Recipharm, Kings Lynn, UK; 2 - Impel Pharmaceuticals Inc, Seattle, WA, USA; 3 - Lonza, Bend, OR, USA; 4 - Proveris Scientific, Hudson, MA, USA; 5 - Faegre Drinker Consulting, Washington, DC, USA; 6 - Intertek Melbourn, Milton Keynes, UK; 7 - Nemera, Lyon, France; 8 - Nanopharm Ltd, Cwmbran, UK; 9 - Nemera, Lyon, France; 10 - Catalent, Morrisville, NC, USA

IPAC-RS International Pharmaceutical Aerosol Consortium on Regulation & Science

Introduction : Existing regulatory guidance concerning intranasal drug delivery is outdated or incomplete. To support product developers and inform the relevant regulatory science, the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) formed a Nasal Working Group (WG) addressing technical, regulatory, and harmonization challenges facing nasal sprays, nasal dry powder inhalers, and nasal pressurized metered dose inhalers. In this poster, two Working Group Subteams present their findings.

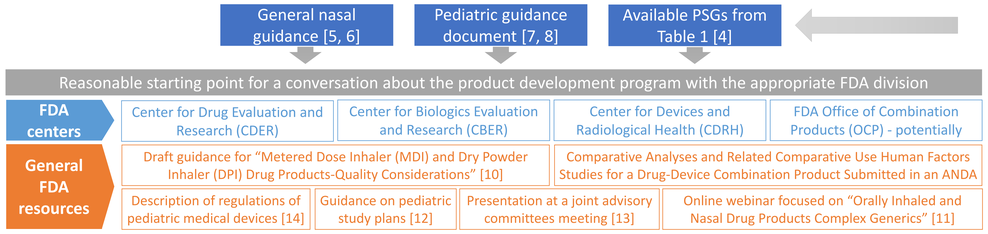
Regulatory Considerations for Nasal Pediatric Products

MATERIALS AND METHODS :

The Nasal Pediatric sub team of the IPAC-RS Nasal Working Group reviewed potentially relevant guidance documents from the US Food and Drug Administration (FDA) and European agencies and summarized currently available resources in this manuscript.

RESULTS AND DISCUSSION : In the US, in preparation for a bioequivalence program for a product under pediatric development when the product is already approved for use in adults, a developer may want to start by searching for an FDA Product Specific Guidance (PSG) available for the generic (or "follow-on") drug and/or dosage form. Typically, the PSGs are not specific to pediatrics, but they could serve as a starting point for building a development program and for planning discussions with the Agency. Patients' age is usually not referenced in PSGs, but it should be considered as a key factor in pediatric product development.

Early dialogues with the Agency are particularly important for nasal products as they are considered by FDA to be drug-device combination products, and as generics they are "complex dosage forms" [9]. In the US, combination products might require consultation with one or more FDA centers (schematic below) in order to have a clear picture of the pathway to a comprehensive submission for FDA review. The FDA Office of Combination Products (OCP) may help coordinate review of combination products by different FDA centers. The need to address aspects unique for pediatric populations adds to this regulatory complexity. When considering a nasal combination product development program, the listed more general FDA resources could also be helpful.



In Europe, the regulatory framework differs from that of the US, and the concepts of "combination product" or "complex dosage form" are absent but general considerations for nasal pediatric product development would parallel those of the US. The European Medicines Agency (EMA) is the main European regulator, issuing guidelines and handling centralized applications. National authorities are involved in cases of mutual-recognition procedures. Unlike in the US, Notified Bodies (i.e., authorized third-party standards setting organizations) are participating in review of applications (in particular, the device portion) and providing opinions for marketing authorizations.

The nasal device part of the product has to comply with the General Safety and Performance Requirements of the Regulation (EU) 2017/745 (EU Medical Device Regulation, Article 117 and Annex I). Depending on how the product is packaged (integral or separately), the device part of a product may need to obtain a CE mark. An early dialogue with relevant regulators (e.g., a scientific advice meeting with EMA) is highly advisable. Similarly to the US, there is no single guideline for nasal pediatric products in Europe – schematic below.

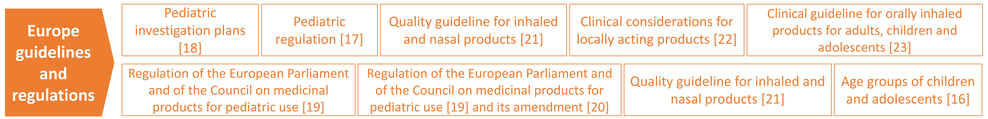


Table 1. Intranasal drug products for which PSGs are available for adults and indicated pediatric age groups [2]

Active Ingredient(s)	Dosage Form	Pediatric Approval		RLD's NDA Number
		Yes or No	Age Range (Years)	
Azelastine Hydrochloride & Fluticasone Propionate	Metered	Yes	4-11	202236
Azelastine Hydrochloride Over the Counter (OTC)	Metered	Yes	6-11	213872
Azelastine Hydrochloride	Metered	No	NA	020114 022203
Beclomethasone Dipropionate	Aerosol, Metered	Yes	4-11	202813
Beclomethasone Dipropionate monohydrate	Metered	Yes	[3] 6	019389
Budesonide	Metered	Yes	[3] 6	020746
Calcitonin-Salmon	Metered	No	NA	020313
Ciclesonide (Zetonna®)	Aerosol, Metered, Nasal	Yes	[3]12	202129
Ciclesonide (Omnaris®)	Nasal Spray	Yes	[3]6 (seasonal), [3]12 (perennial) allergic rhinitis	022004
Cyanocobalamin	Nasal Spray	No	NA	021642
Diazepam	Nasal Spray	No	NA	211635
Dihydroergotamine mesylate	Metered	No	NA	020148
Dihydroergotamine mesylate	Metered	No	NA	213436
Esketamine HCL	Nasal Spray	No	NA	211243
Fentanyl Citrate	Nasal Spray	No	NA	022569
Flunisolide	Metered	No	NA	018148
Fluticasone Furoate	Metered	Yes	[3]2	022051
Fluticasone Propionate	Metered	Yes	[3]4	020121
Fluticasone Propionate OTC	Metered	No	NA	205434
Glucagon	Nasal, Powder	Yes	[3]4	210134
Ipratropium Bromide	Metered	Yes	[3]6	020393 020394
Ketorolac Tromethamine	Metered	No	NA	022382
Metoclopramide HCl	Nasal Spray	No	NA	209388
Midazolam	Nasal Spray	No	NA	211321
Mometasone Furoate Monohydrate	Metered	Yes	[3]2	020762

Reliability Expectations for Emergency-Use Nasal Products

MATERIALS AND METHODS : In the absence of a specific regulatory guidance on this topic, the Nasal Products Reliability sub team of the IPAC-RS Nasal Working Group reviewed the US Food and Drug Administration (FDA) guidance for emergency-use autoinjectors [25]. This poster summarizes the requirements that could be translated to nasal products for emergency use and highlights gap areas where industry and regulators should clarify expectations.

RESULTS AND DISCUSSION :

The main question is **what Design Reliability Development Considerations should be considered for nasal sprays and nasal powders?** To answer this question, the IPAC-RS Working Group proposed that developers of nasal products use relevant information from the autoinjectors guidance [25] and consider additional topics specific to nasal delivery. **Table 2** provides interpretation of the equivalent Essential Performance Requirements (EPR)s for emergency intranasal devices. EPRs are a subset of the device's design input requirements that specify the clinical performance attributes at the point of use that are essential to meet the product's intended use.

It is assumed that reliability expectations would be like the autoinjectors guidance [25], with a top level 'successful spray' (equivalent to 'successful injection') of 99.999% (at 95% confidence) and 99.99% (at 95% confidence) for the other 'secondary' EPR parameters outlined in Table 2. These levels may be subject to revision based on the post-approval data, as more information is gathered through post-market surveillance on nasal products.

For single-use nasal sprays, the functional performance of that device cannot be verified before use, so the semi-empirical Fault Tree Analysis [27] method should be used as part of a predication of reliability ahead of submission. This methodology should remain the same for nasal products as is expected for autoinjectors.

To understand the required pre-conditions to test ahead of the EPRs, the manufacturer should consult ISO 20072 [26], in addition to any relevant foreseeable misuse conditions. This along with the defined supply chain inform the likely stressors that the product will be exposed during the use-life and then captured within the reliability protocol.

Table 2: Emergency-Use Nasal Sprays Design Reliability Development Considerations (for both liquid and powder formulations, unless noted otherwise)

Consideration	Development Examples	Essential Performance Requirements Examples
Top Level	• Device hasn't prematurely actuated • User can actuate the device • Device must deliver a 'spray' on actuation	Successful spray (and Fault Tree Analysis [27])
Protective packaging	• Packaging ability to prevent emergency-use nasal spray damage during shipping, daily carry, etc. • Removal from packaging or carrying case (e.g., force to remove)	N/A
Removal /Deactivation of Safety Mechanism	• Priming of device if needed • Remove any necessary safety mechanisms	N/A
Activation Force	• User can actuate the device • User can apply enough force to generate the required spray characteristics and pump delivery • Device doesn't actuate before use (drop testing / accidental actuation)	• Force to actuate • Force to spray • Minimum actuation force
Spray Characteristics	For Liquid Formulations: • Spray Pattern • Droplet Size Distribution For Powder Formulations: • Particle Size • Geometric size distribution of emitted dose spray	For Liquid Formulations: • Spray pattern parameters • Droplet size distribution parameters For Powder Formulations: • Assessment of aerodynamic particle size
Dose Accuracy	• Intended dose delivered • Shot Weight • Spray Content Uniformity • Pump delivery	Shot Weight (CMC guidance defines spec limits[5])

Conclusions : There is currently limited regulatory guidance specific for **pediatric nasal products** or for **nasal products for emergency use**. Product development teams may find it helpful to examine the existing product-specific guidance for generic nasal products, for emergency-use autoinjectors, and the more general regulatory recommendations for nasal and pediatric products. Based on the review of available guidance's, the IPAC-RS Working Groups are discussing gaps in the regulatory science and potential regulatory approval issues for nasal products and will be identifying opportunities for collaboration and input from industry, pharmacopeias, academia and other stakeholders to develop best practice recommendations.

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REFERENCES

See RDD proceedings for the abstract with full reference listing.

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svetlana.lyapustina@faegredrinker.com