Reliability Expectations for Emergency-Use Nasal Products: IPAC-RS Nasal Subteam Considerations

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Key Message: Nasal sprays for emergency-use are categorised as drug-device combination products, and robustness must be proven to prioritise patient safety. A fundamental task is the classification of design input requirements, and their associated reliability targets. Since specific nasal guidance is lacking, many Essential Performance Requirements (EPRs) can be translated across from the FDA's Emergency-Use Autoinjector guidance and categorised for nasal spray devices.

Introduction:

In the absence of specific regulatory guidance on the topic of emergency use nasal sprays, the Nasal Product Reliability Subteam of the IPAC-RS Nasal Working Group reviewed the US Food and Drug Administration (FDA) guidance for emergency-use autoinjectors [1]. Here, Essential Performance Requirements (EPRs) are introduced, although an exact definition is lacking. It is assumed that they are a subset of design input requirements that specify the clinical performance attributes at the point of use, that are essential to meet the product's intended use. These can therefore relate to the interaction between user and device alongside device performance, although not specific to a particular emergency use application. This study summarised the requirements that could be translated to nasal products for emergency use and highlighted gaps and areas where both industry and regulators should clarify expectations. The identified gaps in guidance were identified as spray characteristics, as well as the specifics of dose accuracy of a nasal spray, such as nasal cast testing, shot weight, spray content uniformity, pump delivery and robustness.

Methods:

The Nasal Product Reliability Subteam of the IPAC-RS Nasal Working Group reviewed the FDA guidance for emergency-use autoinjectors [2] and suggested how these might apply to nasal devices.

Results and Discussion:

To assess the reliability development criteria, the manufacturer must have a clear Target Product Profile (TPP) and user specification to understand the environments, patients and intended uses for their product.

This, along with the supply chain from manufacture to point of use, can then be used to define the "stressors that are likely to occur or to which the product will be exposed to during the use-life" [1]. It is expected that the EPR requirements and subsequent testing, as defined in Table 1, should be performed after this stacked preconditioning sequence to imitate 'real-world' usage.

One of the main questions that arises when reading the guidance for emergency-use autoinjectors is: What Design Reliability Development Considerations should also be considered for nasal sprays (delivering both liquid and powder formulations). In the case of an emergency use nasal spray, it is assumed that the product could be administered by a caregiver, patient or untrained individual and as such should all be considered as sources of risk and misuse.

The IPAC-RS Working Group proposes that developers of nasal products adapt relevant information from the autoinjectors guidance [1], and consider additional topics specific to nasal delivery, as outlined in Table 1. The categories of Protective packaging, Removal/Deactivation of safety mechanisms, Actuation force and Dose Accuracy were taken from the Emergency-Use Injector Design Reliability Development Considerations but modified to be specific to emergency-use nasal sprays. It is assumed that reliability expectations are equivalent to autoinjector guidance [1], with a top level 99.999% for 'failure to spray' (comparable to 'failure to inject', as a binary pass/fail) and 99.99% for the other (continuous data) EPR parameters outlined in Table 1. These levels may be subject to revision based on post-approval data as more information is gathered through post-market surveillance on predicate nasal products.

For single or bi-dose nasal spray devices, where functional performance parameters may not be able to be verified before use, the Fault Tree Analysis method can be used to predict reliability. This is also true for top level 'successful spray' as a binary data output would require an excessive quantity of devices to be tested prior to submission.

Table 1. Emergency-Use Nasal Spray Design Reliability Development Considerations (for both Liquid and Powder Formulations unless noted otherwise)

Category	Development Consideration Examples	Essential Performance Requirement Examples
Top Level	• Device hasn't prematurely actuated • User can actuate the device • Device must deliver a 'spray' upon actuation	• Successful spray (combined with Fault Tree Analysis [3])
Secondary/Protective packaging	**For Liquid Formulations:** • Packaging ability to prevent nasal spray damage during shipping, carrying, etc. • Removal from packaging or carrying case (e.g., force to remove) **For Powder Formulations:** • Packaging must prevent damage to device and environmental impact to powder dose efficacy. • Removal from packaging or carrying case (e.g., force to remove)	• Not applicable
Removal /Deactivation of Safety Mechanism	• Remove any necessary safety mechanisms • Successful priming of device (for relevant device type / application, including shaking for suspensions)	• Not applicable
Actuation Force	• Force to initiate • Force to spray	• Minimum actuation force (as defined by drop testing / accidental actuation) • Maximum force to Actuate (user can always actuate the device) • Force to generate / complete spray (for pumps)
Spray Characteristics	**For Liquid Formulations:** • Spray Pattern • Droplet Size Distribution • Plume Geometry **For Powder Formulations:** • Aerodynamic Particle Size • Geometric size distribution	**For Liquid Formulations:** • Dmin, Dmax, Ovality, Area • Dv10, Dv50, Dv90, Span and %V<10µm **For Powder / Suspensions:** • Aerodynamic particle size • Geometric size distribution
Dose Accuracy	• Nasal cast testing • Pump Delivery (Shot Weight) • Spray Content Uniformity	• Shot Weight (CMC guidance defines spec limits) • Spray Content Uniformity

Conclusions:

There is currently limited regulatory guidance specific for nasal products for emergency use. Based on a review of the guidance documents published to date, gaps have been identified in Spray Characterisation, where further FDA guidance and clarification is required. The Categories of secondary/protective packaging, removal/deactivation of safety mechanism and actuation force have been updated to be specific to the considerations of emergency use nasal sprays. Wider audience feedback is encouraged via the engagement survey QR code on the top right of the poster.

References:

[1] FDA. Draft Guidance for Industry (2020) Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA. [https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-considerations-demonstrating-reliability-emergency-use-injectors-submitted-under-bla-nda] Accessed January 11, 2024

[2] FDA Guidance for Industry (2002): Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products Chemistry, Manufacturing, and Controls Documentation. [https://www.fda.gov/regulatory-information/searchfda-guidance-documents/nasal-spray-and-inhalation-solution-suspension-and-spray-drug-products-chemistrymanufacturing-and]. Accessed January 3, 2024

[3] International Electrotechnical Commission (2012): International standard IEC 61025 (2006-12) Fault Tree Analysis (FTA) https://webstore.iec.ch/preview/info_iec61025%7Bed2.0%7Den_d.pdf Accessed January 8, 2024