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The Preservative Predicament

Nasal sprays have become an important route of delivery for a variety of indications and as their use becomes more widespread, regulatory bodies across the globe have issued various guidelines and recommendations to ensure their safety and efficacy. However, the landscape of these regulations, particularly concerning preservatives, remains complex, leading to confusion and inconsistency of application. This article delves into the current guidance on the use of preservatives in nasal sprays, explores the market trends, and discusses the manufacturing requirements essential for producing safe and effective nasal spray products.

Regulatory Perspectives on Preservatives in Nasal Sprays

In Europe, the regulatory landscape for nasal sprays is influenced significantly by the recommendations of the European Medicines Agency (EMA) and the German Federal Institute for Drugs and Medical Devices (BfArM). Both agencies have recommended the removal of one preservative – benzalkonium chloride (BAK or BAC) – in nasal sprays, citing potential long-term adverse effects on patients. However, it is crucial to note that these are recommendations rather than mandates. The EMA has also updated its requirements for patient labeling on formulations containing BAK, reflecting a growing awareness of preservative-related concerns.[1,2]

Despite these recommendations, there has been no definitive guidance mandating the development of preservative-free nasal formulations. This regulatory ambiguity has led to a perception that the trend towards preservative-free formulations is more of a regulatory compulsion, rather than an industry-driven tendency.

Similarly, the BfArM has echoed the EMA's stance on BAK, recommending its removal but stopping short of enforcing a mandate. This cautious approach highlights the ongoing debate within regulatory circles about the necessity and feasibility of eliminating preservatives from nasal formulations.

Across the Atlantic, the U.S. Food and Drug Administration (FDA) has provided more detailed guidance on various aspects of nasal spray development. According to the latest FDA guidelines, numerous factors need to be considered during the development program of nasal sprays. These include formulation, container closure systems, manufacturing processes, stability, and controls of critical steps and intermediates. The FDA emphasises that any changes in these aspects can significantly impact the product's ability to deliver reproducible doses to patients throughout its shelf life but stops short of recommending or issuing guidance on removing preservatives in formulations.[3,4]

The FDA acknowledges that if a formulation is preservative-free, it requires the use of a preservative-free device designed to prevent microbial ingress. This can be achieved using .22 sterile filters and other closure mechanisms in the nasal devices.[5]

The global regulatory landscape for nasal sprays reflects a cautious and evolving approach towards preservative-free formulations. Although there is a tendency towards such formulations, there is still no clear mandate from regulatory authorities. This ongoing debate underscores the need for continuous review and adaptation of manufacturing practices to meet both regulatory expectations and market demands.

Current Market Landscape for Nasal Sprays

Until recently, nasal sprays have been primarily used for treating allergies, rhinitis and sinusitis, with products ranging from over the counter (OTC) products to prescription (Rx) decongestants, antihistamine and anti-inflammatory products. The largest class of commercially available medicines are the nasal corticosteroids, or nasal steroid sprays, with drugs such as fluticasone, mometasone, and triamcinolone.

Since the late 1990s, intranasal drug delivery for systemic indications, especially for rescue therapies, have overshadowed all commercial approvals. This is due to a rapid onset of action of the drug, ease of administration and convenience as opposed to injections, oral delivery or other routes of administration. Indications range from treatment of opioid overdose, migraine, seizure, anaphylaxis and a variety of other indications. Many of today's leading Rx nasal sprays, some of which are now OTC, utilise preservatives like benzalkonium chloride and sodium phosphate, to ensure their stability and efficacy over time (Table 1).

In the United States, there are only five products that are preservative-free: Migranal®, Noctiva®, Nayzilam®, Rivive® and Zavpret®. Of these five only one appears to be manufactured in sterile conditions – Noctiva. Specifically, the approved labeling states "nasal sprays are not typically required to be sterile. Noctiva is manufactured under aseptic conditions but becomes non-sterile once in use. The device adequately prevents ingress of bacteria, which is important because the product does not contain a preservative and bacterial contamination could degrade desmopressin".[7] The other products specifically state they are "non-sterile" and/or submitted to the appropriate microbial growth controls during the manufacturing process.[8,9,10,11]

While it may appear that there is a shift towards preservative-free nasal sprays, it is evident that this trend is more driven by industry innovation and consumer preference rather than stringent regulatory requirements. The perception of a strong movement towards preservative-free formulations needs to be balanced with the reality of regulatory guidance and market reality.

Manufacturing Requirements for Nasal Sprays

Manufacturing nasal sprays involves adhering to several key requirements to ensure product safety, efficacy, and quality. The FDA's guidance on nasal spray manufacturing emphasises the critical need to ensure that the product can deliver consistent and reliable doses with the highest quality throughout its shelf life. This involves rigorous attention to formulation, container closure systems, manufacturing processes, stability, and process controls at every stage of production. Each of these aspects must be tailored and maintained to the specific product requirements to sustain its efficacy and safety.

Developing preservative-free nasal sprays introduces additional complexities, which

Reference Drug	Molecule	Indication	Preservative	Year Approved
Flonase® and generics	fluticasone propionate	perennial allergic or nonallergic rhinitis	benzalkonium chloride	1994 OTC in 2003
Nasarel®	flunisolide	seasonal or perennial rhinitis	benzalkonium chloride	1995 (discontinued)
Afrin® and generics	oxymetazoline hydrochloride	relief of nasal congestion	benzalkonium chloride	1966 OTC in 1975
Nasacort® and generics	triamcinolone	seasonal and perennial allergic rhinitis	benzalkonium chloride	1996 OTC in 2013
Nasonex® and generics	acetonide	seasonal allergic or perennial rhinitis	benzalkonium chloride	1997 OTC in 2022
Migranal® and generics	mometasone furoate	acute treatment of migraine	none	1997
Imitrex® and generics	sumatriptan	acute treatment of migraine	Sodium phosphate	1997
Rhinocort® and generics	budesonide	seasonal or perennial allergic rhinitis	potassium sorbate	1999 OTC in 2015
Zomig® and generics	zolmitriptan	acute treatment of migraine	Sodium phosphate	2003
Dymista® and generics	azelastine hydrochloride and fluticasone propionate	seasonal allergic rhinitis	benzalkonium chloride	2012
Narcan® and generics	naloxone	opioid overdose	benzalkonium chloride	2015
Xhance®	fluticasone propionate	chronic rhinosinusitis without nasal polyps.	benzalkonium chloride	2017
Noctiva®	desmopressin	nocturia due to nocturnal polyuria	none	2017
Tosmyra®	sumatriptan	acute treatment of migraine	Sodium phosphate	2019
Spravato®	esketamine hydrochloride	treatment resistant depression and depressive symptoms in adults with MDD with acute suicidal ideation or behavior	edetate disodium	2019
Nayzalam®	midazolam	acute treatment of seizures	none	2019
Valtoco®	diazepam	acute treatment of seizures	benzyl alcohol	2020
Tyrvaya®	varenicline	dry eye disease	Sodium phosphate	2021
Kloxxado®	naloxone	opioid overdose	Dehydrated alcohol 20%	2021
Opvee®	nalmefene	opioid overdose	benzalkonium chloride	2023
Rivive®	naloxone	opioid overdose	none	2023
Zavzpret™	zavegepant	acute migraine	none	2023
Neffy®	epinephrine	emergency treatment of allergies/ Anaphylaxis	benzalkonium chloride, disodium edetate	2024

Table 1. Rx and OTC Nasal Spray with Type of Preservative in the Formulation[6]

require adherence to stringent guidelines to ensure patient safety. These formulations have a unique set of requirements that pose significant challenges. These challenges include the following: advanced formulations techniques, sterile environmental handling, processing, controls, and the use of delivery devices capable of maintaining sterility. Additionally, these formulations require thorough risk assessments and validation studies to demonstrate that the product can maintain sterility and efficacy throughout its shelf life.

Nasal sprays can be confidently manufactured utilising a preserved formulation or a preservative free formulation with a sensible approach to risk. The following techniques minimise bioburden to ensure one can produce a product of the highest quality.

- **Aseptic Techniques:** Mimicking conditions before and during the transfer of formulations into nasal delivery devices is critical. This includes the use of single-use disposable vessels and tubing during compounding and filling processes.
- **Low Bioburden Grade C Environment:** Manufacturing in a controlled Grade C environment helps minimise microbial and particulate contamination. This baseline allows for limited to no environmental impact to the formulation.
- **Dedicated Single-Use Product Contact Pieces:** Using dedicated single-use contact pieces wherever possible further reduces contamination risks.
- **Closed System and Sterilisation Filtration:** The manufactured solution post-sterilisation filtration remains within a sanitised system (hold vessel, single use tubing, filling needles) until moment of fill. Ultimately, limiting exposure to the open Grade C environment to seconds prior to stoppering/capping. between filling and stoppering/capping of finished product.
- **Personnel Practices:** Personnel must adhere to strict aseptic techniques, including the use of personal protective equipment (PPE) and rigorous cleaning practices.
- **Terminal Sterilisation:** Techniques such as radiation can

be used to inactivate any potential microbial contamination post-filling.

Cost Implications and Benefits of Low Bioburden Manufacturing

Drug development companies need to evaluate how the chosen production pathway of their drug candidate and the related costs of such will impact its commercialisation success. For example, the cost implications of manufacturing nasal sprays, particularly preservative-free formulations in sterile conditions, are substantially higher than those of preserved formulations and will lead to a higher cost of goods (COGS) and can directly impact the profitability of the product for commercialisation. Sterile manufacturing of nasal products is also not as widely available, thus limiting third-party manufacturing options. Low bioburden manufacturing, as before, is generally less expensive than sterile manufacturing, offering a cost-effective alternative while still ensuring high levels of safety, quality, and efficacy.

Adopting low bioburden manufacturing techniques can provide several benefits for drug companies. It allows them to meet regulatory and market demands for preservative-free products without incurring the higher costs associated with sterile manufacturing. Also, it supports producing high-quality nasal sprays safe for acute and chronic use by patients.

Conclusion

In the evolving landscape of nasal spray manufacturing, regulatory recommendations and market trends are shaping the development of preservative-free formulations. While the debate on preserved or preservative-free continues, the industry must assess what is best for the drug candidate considering current recommendations and consumer preferences. As a contract development and manufacturing organisation (CDMO), our role is to support innovators in navigating these complexities, offering expertise in both traditional and preservative-free nasal spray manufacturing. By leveraging advanced aseptic techniques and ensuring low bioburden levels, CDMOs help clients achieve their formulation goals while maintaining the highest standards of safety and efficacy.

The future of nasal sprays will see continued innovation and adaptation as regulatory bodies refine their guidelines and the market evolves. In the meantime, a comprehensive understanding of current requirements and best practices remains

essential for successful product development and patient care.

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