PATIENT SAFETY: KEY DRIVER TO PRESERVATIVE-FREE NASAL SPRAY DEVELOPMENT

In this article, Benoît Guillard, Product Development Leader, Pascale Farjas, Global Category Manager – ENT, and Audrey Chandra, Global Category Manager – Inhalation and Dermal, all of Nemera, look at the effects of preservatives in nasal sprays, and the challenges and advantages of delivering preservative-free nasal spray drugs.

Current challenges in treating patients who suffer from chronic diseases have encouraged pharmaceutical companies to continue innovating to tackle the problems encountered by patients. The quality of life of these patients depends highly on their clinical outcomes, which are based on their adherence to the prescribed treatment as well as on the efficacy of their treatment.

The adverse effects of treatment may affect patient compliance. For example, the use of preservatives in a nasal spray may affect patient adherence due to its risks and possible side effects. Innovation in nasal delivery therefore becomes a crucial need for patient safety. By using a preservative-free nasal spray on a daily basis, patients should worry less about the adverse effects of their treatment – which therefore encourages better patient compliance.

THE EFFECTS OF PRESERVATIVES IN NASAL SPRAY

If we take a closer look at nasal drug products delivered through a device for chronic diseases, it mainly concerns locally acting drugs for allergic patients – i.e. nasal sprays. The nasal mucosa plays an important role in mediating immune responses to allergens and infectious particles which enter the nose. It helps prevent allergens and infections from invading the nasal cavity and spreading to other body structures – for example, the lungs.

The nose cavity is lined with a type of epithelium where cells arrange themselves in columns and project tiny hairs called cilia which contain mucus-producing cells (goblet cells). Different types of preservative found in nasal sprays may have different undesirable side effects on the physiology of the nose cavity, which are observed in various studies.

However, the use of preservatives in nasal sprays has become controversial. Some argue that a certain amount is well tolerated by patients, whereas others state that they might increase the risk of adverse events for patients. For instance, an *in vitro* study shows that benzalkonium chloride (BAC) can cause ciliotoxicity (impaired ciliary activity) of the nasal mucosa – and therefore nasal irritation.[1]

In a wide range of clinical trials, which used mostly nasal sprays containing BAC, various adverse effects have been observed. These side effects include increased mucosal swelling and nasal hyper-reactivity, type IV hypersensitivity, decrease of mucociliary clearance, and nasal mucosa dysplasia. On the other hand, some clinical studies claim no effect on ciliostatic and no toxic effect.

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Although the use of preservatives in nasal sprays is debatable, risks have

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been reported by different studies and, consequently, the European Medicine Agency (EMA) recommends zero BAC in nasal sprays. In fact, the German Federal Institute for Drugs and Medicinal Devices (BfArm) has proposed that BAC is removed from intranasal products in Germany because of concerns about mucociliary effects.[2] Keeping in step with the regulatory trend, and applying the precautionary principle for patients, Nemera has developed preservative free approaches.

KEY BENEFITS OF ADVANCIA® PF WITH PUREFLOW TECHNOLOGY

Driven by the regulatory recommendations for preservative-free formulations in nasal sprays, as well as the desire to protect patients from adverse events, a technology breakthrough is a fundamental requirement when designing a preservative-free drug delivery device. Instead of using preservatives, an alternative way of keeping a nasal spray sterile is by preventing bacteria entering and contaminating the drug formulation.

Nasal sprays can be contaminated through their drug delivery orifices, with bacterial contamination coming from the external environment or the patient. A mechanical closing tip ensures that no contamination can be introduced in the nasal spray orifice after the spray has been dispensed.

To prevent contamination via air entering the device, most commercialised nasal sprays use a filter system which stops the entry of bacteria into the container. Airborne bacteria are typically around 0.3 µm. However, other smaller bacteria are present.[3] Furthermore, recent studies have demonstrated that bacterial transfer through the membrane structure takes place during filtration operations, even if the pore size is significantly smaller than the bacteria size.[4]

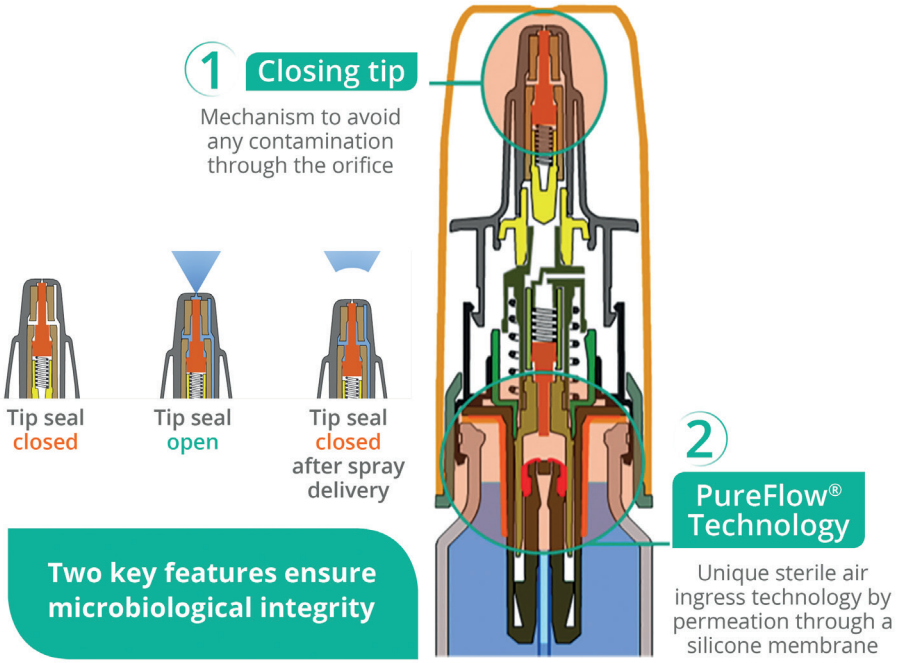

Figure 1: Advancia® PF illustration.

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Nemera has introduced an alternative to filters for the Advancia® PF (Figure 1) nasal spray – using a silicone membrane to filter the returning air. The intake of air into the dispenser takes place via a venting system with a silicone membrane called PureFlow technology (Figure 2). This patented technology has a continuous barrier of homogenous material which allows air to diffuse through the silicone, which acts as a permeable membrane. Consequently, the continuous barrier guarantees the microbial integrity of the drug.

The venting system filters the intake of air using a very fine membrane manufactured from silicone polymer. The silicone membrane is a solid, non-porous material. As it is homogenous and does not contain any holes, it can be precisely engineered. The membrane's intermolecular distance is of the order of nanometres – allowing the passage of air through the membrane but completely preventing the passage of any liquid or solid particle, including bacteria, due to the silicone membrane structure where the size is smaller than 0.3 µm.

The function of the silicone membrane can be compared to an inflated balloon. The balloon is a continuous, waterproof material yet gas slowly passes through the wall of the balloon until the pressures inside and outside reach equilibrium. Devices that use this technology can be

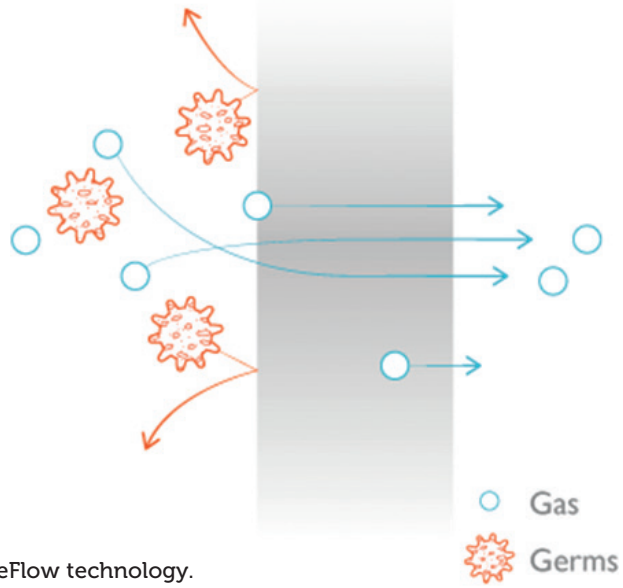

Figure 2: PureFlow technology.

tested individually in-line as a consistent part of the manufacturing process to ensure robust quality standards. This provides an even greater assurance of safety for patients.

Moreover, Advancia® PF offers a patented anti-clogging actuator in the upper part of the system, called closing tip. This mechanism ensures that no contamination can enter through the actuator orifice, which therefore provides protection from crystallisation and clogging issues, and avoids evaporation to guarantee good prime retention.

PERFORMANCE EVALUATION OF ADVANCIA® PF

To assess the performance of Advancia® PF, the microbial integrity has to be evaluated by two common practice methods.[5,6] The first standard contamination test is done by immersing the applicator inside a contaminated petri dish. The second test uses a contaminated air suspension which contains bacteria. These tests are used to verify the performance of the nasal spray; to prove whether or not the formulation inside the nasal spray is contaminated after repeated spray actuations.

The closure venting integrity test (Figure 3) is done by using *Bacillus subtilis* with a concentration between 10^8 and 10^9 CFU/g on an anti-static spherical aerosol size of a few µm. The test protocol requires nutritious sterile solution and the test has to be done on 20 samples.

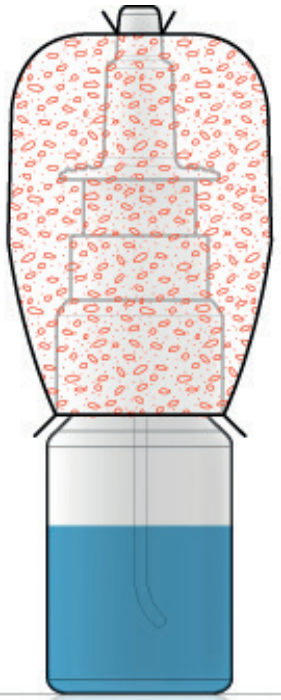

Figure 3: Closure venting integrity test.

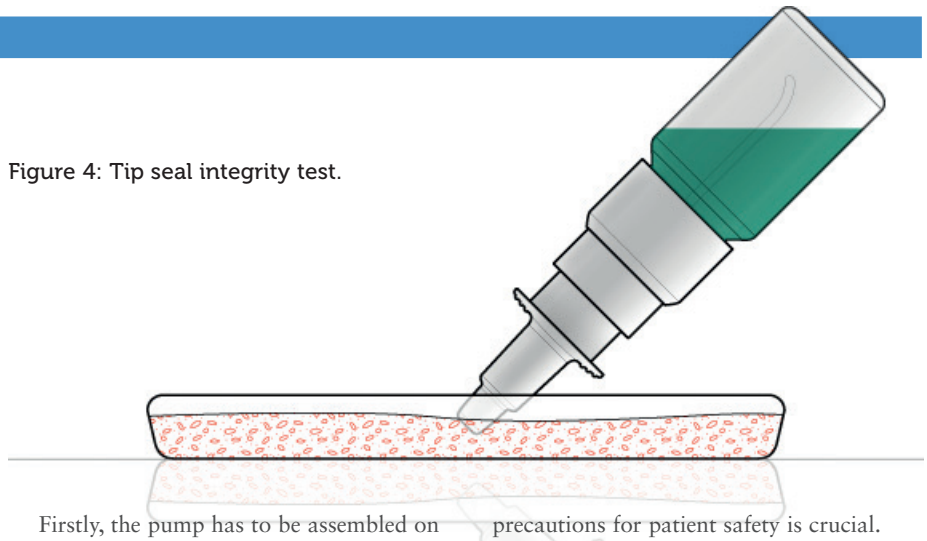

Figure 4: Tip seal integrity test.

Firstly, the pump has to be assembled on a bottle. Then, the sterility of the assembly must be checked after the assembly of the device, before exposure to the bacteria, with an incubation conducted for several days at more than 30˚C. Finally, an elastomeric sleeve has to be put around the pump and vial, and the gap between the pump and the vial is filled with the contaminated powder. The sleeve is sealed to the pump and vial. The pumps are actuated a number of times and the sterility of the nutritious solution is checked, with incubation for several days at more than 30°C. The test will therefore show whether the solution is contaminated or not.

The second contamination test is called a tip seal integrity test (Figure 4) and uses *Pseudomonas aerugiosa* with a concentration of 10^7 CFU/ml in a sterile peptone water solution inside a petri dish. The test is also done on 20 samples. The pump is assembled on a bottle filled with peptone water and incubated for several days at more than 30˚C to check the microbial contamination of the device following assembly and before exposure to the bacteria. Over the course of eight days, the pumps are actuated a number of times – with the orifice tip of the nasal spray immersed in a contaminated solution – and some sprays are collected in a petri dish to evaluate contamination of the spray. This test is done to check if the spray has any microbial load.

All 20 pumps of Advancia® PF with PureFlow technology passed both the tests – the closure venting integrity test and the tip seal integrity test – since no bacterial ingress in the container or on the tip was observed.

ENSURING PATIENT SAFETY THROUGH ADVANCIA® PF

Patients should be the key driver for innovation breakthroughs as patient safety should be the number one priority. Understanding what are the pain points for the patient is an important element in nasal spray development. Implementing different precautions for patient safety is crucial.

In the case of patients using nasal sprays daily over several weeks – for instance, to relieve allergy symptoms – it makes sense to keep preservatives away from the formulation to avoid adverse effects such as nose irritation. Applying this precautionary principle for patients, Nemera has therefore developed Advancia® PF to deliver preservative-free nasal spray drugs, as well as to keep up with the regulatory trend.

ABOUT THE COMPANY

Nemera is one of the world's leading designers, developers and manufacturers of drug delivery devices for the pharmaceutical, biotechnology and generics industries. It uses different types of business model including full solution development, pure contract manufacturing and customised solutions.

Nemera's areas of expertise include numerous modes of delivery: parenteral, nasal, buccal, auricular, ophthalmic, pulmonary, dermal and transdermal. The company has more than 150 engineers working in development, sales in 47 countries, over one billion devices produced yearly, and more than 1,950 employees.

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ABOUT THE AUTHORS

Benoît Guillard graduated at the National Institute of Applied Sciences of Lyon (France) and studied at the Trinity College of Dublin (Ireland). He holds a double master degree in mechanical engineering and in biomechanics. After several experiences with product development leadership role in the medical and pharmaceutical industry, he joined Nemera in 2014, where today he leads teams of engineers for the development of new nasal drug administration systems, within Nemera's Insight Innovation Center. In his role he contributed to the commercial launch of Advancia® and he is now focused on Nemera nasal product line extension and customer product developments. He has a successful track record of marketed drug delivery systems and medical devices, and an in-depth knowledge of these high technology product development, their large-scale production and the associated pharmaceutical industry regulation.

Pascale Farjas is the Global Category Manager for the ENT (ear, nose, and throat) segment at Nemera. Her role encompasses understanding patients' needs and regulatory requirements to develop and market packaging solutions that improve the patient experience. She is in charge of the market introduction of new pump platforms for nasal sprays. Ms Farjas joined Nemera in 2011 and holds a chemical engineering degree from the National Institute of Applied Sciences of Rouen, France, completed with a marketing-focused Master Degree from the Business Administration Institute (France). Prior to joining Nemera, Ms Farjas held various positions in strategic (market intelligence and market studies) and operational marketing in the pharmaceutical industry for international markets.

Audrey Pamila Chandra joined Nemera in February 2019 as the Patient Media Watch Analyst and has now become the Global Category Manager for the Inhalation and Dermal segment in Nemera. She believes that the ease of use of the device plays an important role in patient quality of life. She is in charge of identifying the pain points and the unmet needs of the patients, and also accompanying product development in parallel. Ms Chandra graduated from the Faculty of Medicine in Indonesia and she pursued her Master studies in Strategy and Business Development in Toulouse School of Management, France.

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