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INFLUENCE OF THE HUMAN FACTOR ON NASAL DRUG DELIVERY DEVICE EVALUATION

In this article, Pascale Farjas, Global Category Manager, Alain Regard, Technology Product Manager, and Guillaume Grevin, Senior Design Engineer, all of Nemera, discuss what is required of a modern nasal spray pump and how introducing the human factor to a study of five nasal spray pumps, including Nemera's own Advancia device, showed a significant impact on the variability of delivered volume.

INTRODUCTION

Intranasal delivery is a common route of administration for treating various indications, from allergic rhinitis to breakthrough cancer pain. On the one hand, nasal delivery is an attractive option for locally acting medications (e.g. saline solutions, decongestants, corticosteroids or antihistamines) which treat allergic rhinitis and nasal congestion. On the other, the nose is also the entry point for systemic delivery of numerous drugs and therapies for a variety of diseases. In these cases, common drugs used include calcitonin (osteoporosis), fentanyl, triptans (pain management), estradiol (hormone replacement therapy), nicotine (smoking cessation), desmopressin (enuresis), and metoclopramide (motion sickness).[1]

> "Ever more drugs targeting other therapeutic fields and diseases may join the increasing ranks of marketed products for systemic delivery using the nasal route, such as drugs that act upon the central nervous system to treat disorders like Alzheimer's disease and obesity."

Ever more drugs targeting other therapeutic fields and diseases may join the increasing ranks of marketed products for systemic delivery using the nasal route, such as drugs that act upon the central nervous system to treat disorders like Alzheimer's disease and obesity.[2] The main reason for this trend in achieving systemic delivery via the nasal route is the advantage of delivering treatments directly from the olfactory region into the brain, allowing the drug to circumvent the blood-brain barrier.

Furthermore, nasal vaccination is an attractive alternative to injection that causes little discomfort to patients. Mucosal vaccines not only promote good local immune protection, but also a systemic response similar to that of injection.[3] FluMist® (MedImmune (AstraZeneca), Gaithersburg, MD, US), is a nasal influenza vaccine currently on the market and is a popular alternative to the traditional influenza vaccine injection, particularly for children.

Also, preservatives, such as benzalkonium chloride, are commonly used in nasal drug formulations. However, preservatives can irritate the mucosa, deteriorate ciliary clearance and cause unpleasant adverse effects, such as itching, which may negatively impact compliance. For instance, long-term use of intranasal corticosteroids with benzalkonium chloride can lead to high-grade dysplasia in the nasal mucosa.[4] The development of preservative-free nasal medications is especially important for chronic treatments which, by their nature, require daily use over several months (e.g. for allergic rhinitis therapies) and require appropriate multi-dose delivery systems that prevent contamination.

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Nemera has developed a new preservative-free nasal pump, designed to increase compliance and deliver a precision dose independent of user actuation profile, ensuring the full dose is administered every time.

HOW IS THE PERFORMANCE OF A NASAL SPRAY PUMP DEFINED?

Nasal spray pump performance can be evaluated in accordance with different regulations, such as those set out by the EMA, US FDA or one of the pharmacopeias. Physical characteristics of the spray are then measured with precise methods.

- **Dose delivery**, or shot weight, consists of single actuation weighing and gives information about the consistency of dose delivered to the patient.
- **Droplet size distribution** is measured by laser diffraction.
- **Particle size** is measured by cascade impactor.
- **Spray geometry** consists of the plume geometry and spray pattern measurements.

These characteristics are also important for evaluating the performance of the pump in order to predict nasal deposition. In particular, taken together the droplet size distribution and particle size measurements inform about the overall particle size distribution of the spray, enabling prediction of how the spray deposits in the airways.

Although these physical parameters are relevant to describe the spray produced by nasal pump, *in vitro* spray characteristics evaluated in accordance with different standards/guidelines are mainly assessed using automatic spray actuation controlling the velocity, timespan and strength of actuation. This is restrictive as it does not mimic the variation in actuation profile demonstrated by humans. Previous studies have demonstrated the influence of the actuation parameters on spray characteristics,[5] questioning the robustness of standard *in vitro* methods for predicting the spray performances when, in practice, the device is manually actuated by patients.

EVALUATION TAKING INTO ACCOUNT THE HUMAN FACTOR

Nemera proposed a study in which the evaluation of intranasal delivery devices took into account the human factor. First, Nemera evaluated the dose delivered under real use conditions with volunteers. *In vivo* measurements were taken in terms of delivered volume via manual actuation for evaluating the influence of the human factor on the variability of the nasal spray pump's performances. The same devices were then evaluated using an automatic actuator system to measure the delivered volume as per standard methodology. *In vivo* and *in vitro* results were then compared to determine *in vitro*/*in vivo* correlation.

The delivery system is a critical element for nasal spray performance, in particular it needs to deliver a uniform dose upon each actuation. Hence, the device must be user-friendly and convenient for "on the go" use so that the patient can rely on the nasal spray at any time during the treatment, especially during a migraine or allergy related symptoms, which often occur outside the convenience of the patient's home.

Furthermore, adherence is a key parameter which can influence the efficacy of the treatment. Indeed, not only should the therapeutic efficacy and molecule safety be taken into account for a treatment, but ease of use and comfort of the dispensing system for the patients as well. The nasal spray should help the patient to accept the treatment and therefore improve patient compliance. To achieve patient acceptance and improved compliance, ergonomics should be applied to the nasal device design to ensure overall attractiveness and user-friendly features, such as intuitive handling, good grip, uniform delivery accuracy regardless of actuation profile, etc. These attributes should allow the patient to use the device properly and receive their daily dose of medication required, by improving overall patient compliance.

As with all self-administered drugs, the most critical parameter affecting device performance is the patient themself. A patient, most of the time untrained, relies on their personal appreciation and the instructions for use to operate the device properly. This perspective constitutes the fundamentals of Human Factors Engineering (HFE),[6,7] an inclusive design process that aims to identify and mitigate all user-induced risks. The HFE process is based on user studies to identify risks and user misunderstandings, then improve the device design accordingly. HFE also highlights user competence and satisfaction as equally important in ensuring patients' adherence to their treatment. Verifying both a safe and user-friendly device eventually relies on a combination of very different factors; ranging from functional to more perceptive ones, such as overall ergonomics or daily-use adaptability.

In the second step of this study, Nemera evaluated the performance of the devices in terms of perception and feeling because even the best drug, in the best container, with the best delivery device, can end up being useless if patients don't, or can't, use it properly.

IN VIVO STUDY

Thirteen healthy adult volunteers (seven male, six female) were included in this single-centre study (Figure 1). The study was performed in 2017 at Nemera (Innovation Center, La Verpillière, France). Five different nasal spray pumps from different companies were filled with water and were tested in a randomised order,

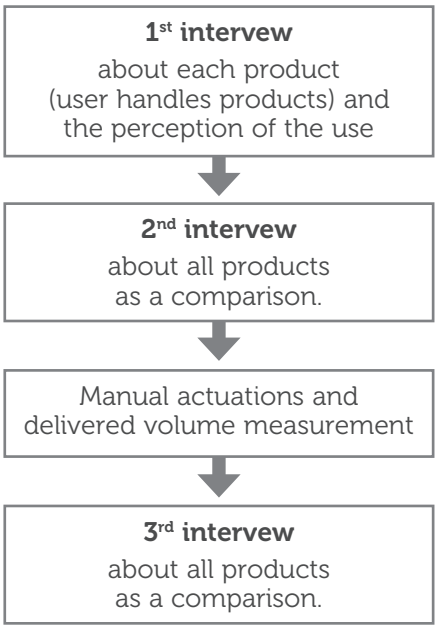

Figure 1: *In vivo* study protocol.

Figure 2: *In vivo* volume delivery test with Advancia nasal pump.

Figure 3: *In vitro* volume delivery test with Advancia nasal pump.

including Nemera's own next-generation pump, Advancia (Figure 2). A first interview was conducted with the volunteers before the test. Each product was observed and manually manipulated. A second interview was conducted for product comparison. The device was manually primed and then given to the healthy volunteer. The device was actuated in ambient air and the weight difference was measured to calculate the delivered volume by the volunteers. Three actuations were performed per device and per user, resulting in 39 results per nasal pump. After the five pumps were tested manually by the volunteers, a last interview was conducted about the five nasal pumps. Participants were asked to rank the different nasal pumps in three boxes: the green box (for those they would like to use for a long-term daily treatment), the red box (for those they wouldn't like to use for this treatment) or the yellow box (for those in between). Results to these questions gave a ranking from the most appreciated pump to the least appreciated one.

IN VITRO STUDY

The same devices used in the *in vivo* study (provided from the same batches) were tested in a randomised order in an *in vitro* study (Figure 3). They were filled with water and manually primed. Devices were placed in an automatic actuator (Proveris NSx, actuation speed of 80 mm/s, acceleration of 7000 mm/s²). Devices were actuated in ambient air and the weight difference was measured to calculate the delivery volume. 39 actuations were performed per device to match the number performed in the *in vivo* study.

RESULTS

Figure 4 clearly shows how the volunteers ranked the different pumps. Advancia proved to be the pump that volunteers felt most positively about, with no appearances in the red box and almost 70% of the time being placed in the green box (nine in the green box). Contrarily, Devices A and B were the two pumps that the volunteers felt the least affinity for (one and two in the green box respectively).

Figure 5, and the associated data in Table 1, shows the mean average of the delivered volume across the devices for the *in vitro* and *in vivo* studies. All products have a relatively low *in vitro* variability, with a maximum of 5% for device B and a minimum of 0.6% for device D. However, manual actuation by the 13 volunteers shows larger variability in terms of delivered volume, with the exception of Advancia (device E). There was a good correlation between the mean of *in vitro* delivered volume (x) and the mean of the *in vivo* delivered volume (y) (y=0.93x, R^2=0.97). Nevertheless, Figure 5 shows a trend towards lower volumes delivered by manual actuation, most keenly observed in device D, with a dose decrease of 12% between *in vitro* and *in vivo* actuation.

Regarding data dispersion, we can observe a high user dependency on volume delivery for devices A, C & D, around 25% in terms of variability, and a lower user dependency for devices B and E (Advancia), around 5% in terms of variability. These results confirm the influence of a manual actuation of the device on delivered volume variability.

CONCLUSION

A correlation in terms of mean delivered volume was found between *in vitro* and *in vivo* tests, showing a lower delivered volume by manual actuation in comparison to automated actuation (-7%). Different manual actuations by users were visually observed, explaining a partial delivered volume from the device when the actuation was incomplete. Furthermore, a high difference in terms of delivered volume variability was observed between *in vivo* and *in vitro* results, demonstrating the difficulty of predicting real device variability from automatic actuation only. Nemera's Advancia device was the only device to show a good correlation between *in vitro* and *in vivo* results in terms of delivered volume and variability.

Regarding the user satisfaction for the five nasal pumps, nine out of the thirteen volunteers said they would prefer using the Advancia device for a long-term treatment, more than for any of the other devices in this study. However, whilst Advancia had the best results both in terms of the user satisfaction test and delivered volume variability, interestingly there was no overall correlation found between patient satisfaction and spray volume variability.

The conclusions drawn from this study have limitations, in particular with regard to the low number of participants who tested devices, and therefore complementary tests should be performed in order to confirm these results. However, similar conclusions have been obtained by droplet size distribution

Participants were asked to rank all nasal pumps into one of three categories:

- green (for those they would like to use for long-term daily treatment)
- red (for those they wouldn't like to use for this treatment)
- yellow (for those in between)

Figure 4: Results from interviewing the 13 volunteers.

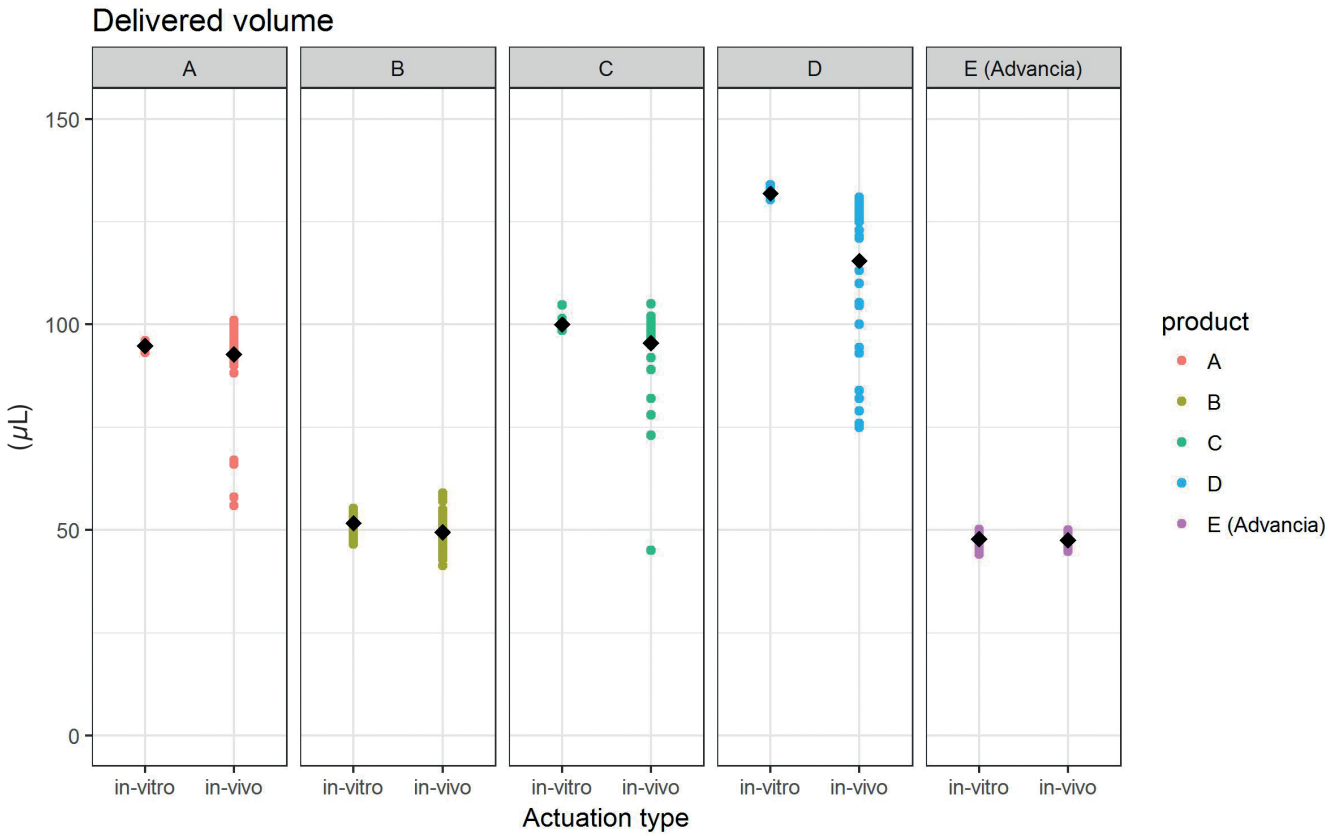

Figure 5: Volume delivery by automated actuation (*in vitro*) and by manual actuation (*in vivo*) for the five nasal pumps (n=39 actuations per device) with the mean value shown in black.

	In vitro			*In vivo*		
Device	Mean (µL)	SD (µL)	Min-Max (µL)	Mean (µL)	SD (µL)	Min-Max (µL)
A	95	1	93-96	92	12	56-101
B	52	3	47-55	50	5	41-59
C	100	1	99-105	96	10	45-105
D	132	1	130-134	116	19	75-131
E (Advancia)	48	1	44-50	48	1	45-50

Table 1: Volume delivery by automated actuation (*in vitro*) and by manual actuation (*in vivo*) for the five nasal pumps (n=39 actuations per device) in terms of mean, standard deviation (SD) and minimum-maximum (Min-Max).

measurement,[8] showing a higher variability in terms of droplet size by manual actuation compared with automated action.

Nevertheless, an automatic actuator is recommended by multiple regulatory agencies for spray performance evaluation. This may be due to automatic actuation having the advantage of being able to evaluate variation associated with different batches of drug product. Furthermore, controlling the actuation force or the velocity can help to give a better understanding of the inherent device performance by eliminating them as variables. Therefore it can be stated that an automatic actuator is a good option for evaluating device quality but seems poorly suited for predicting *in vivo* results.

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ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacturing of drug delivery devices for the pharmaceutical, biotechnology & generics industries.

Nemera's services and products cover several key delivery routes:

- Nasal, Buccal, Auricular (pumps, valves and actuators for sprays),
- Ophthalmic (multi-dose, preservative-free eyedroppers),
- Inhalation (pMDIs, DPIs),
- Dermal and transdermal (airless & atmospheric dispensers),
- Parenteral (auto-injectors, pens, safety devices & implanters).

Nemera always puts patients first, providing the most comprehensive range of devices in the industry, including innovative off-the-shelf systems, customised design development and contract manufacturing.

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Pascale Farjas is the Global Category Manager for the ear, nose, and throat (ENT) segment at Nemera. Her role encompasses understanding patient 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 Masters 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.

Alain Regard, Technology Product Manager, graduated with a degree in Polymer Engineering and Processing from ESP in Oyonnax, France. After a long experience in design and development in the automotive industry, he joined the company in 2010 as a product development leader. Mr Regard, today one of the key technical experts of Nemera's Innovation Center for Devices (ICD), leads the nasal and dermal developments. He drives some of Nemera's own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

Guillaume Grevin, Senior Design Engineer, graduated from ISPA, Alençon, Normandy in Industrial Plastics. In 2008, after gaining experience in the plastic films industry, and in medical primary packaging R&D, he took part in the transformation of Nemera's R&D department into the Innovation Center. After a major role in the development of an innovative ophthalmic platform, Guillaume has been strengthening its expertise in nasal segment since 2012. Today he contributes both to the development of Nemera's own IP projects and upscaling product knowledge.

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