Nemera

BIOEQUIVALENCE FOR NASAL SPRAYS: IMPORTANCE OF DEVICE PERFORMANCE

Here, Pascale Farjas, Global Category Manager ENT Products, Nemera, describes the company's Device Equivalence Program, which enables Nemera to preselect and propose an appropriate delivery system per identified drug to companies wishing to save time in their nasal spray development pipeline.

The most common use of multi-dose nasal sprays is for allergy related symptoms, such as allergic rhinitis. We will focus on nasal preparations for the administration of locally acting drugs (e.g. nasal steroids, nasal decongestants). Because the efficacy of the drug depends upon the spray device's ability to deliver a uniform dose as well as a reproducible droplet size and plume, the delivery system is a critical element for nasal spray performance.

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Nemera has established a Device Equivalence Program in order to respond to market enquiries in terms of nasal spray equivalence and second-sourcing needs. Nemera's main objective is to preselect and propose an appropriate delivery system per identified drug to companies wishing to save time in their nasal spray development pipeline. The program features:

- A preliminary bioequivalence study: de-risking approach to speed-up project development
- High-level protocol and robust statistical approach based on the EMA and US FDA guidelines
- Specific methodology to support "performance matching" activities in nasal sprays
- A cutting-edge laboratory for device performance *in vitro* testing support.

The Device Equivalence Program process is summarised in Figure 1.

Nemera's standard platform for nasal sprays comprises the SP270+ pumps range and various nasal actuators (Figure 2). The new optimised SP270+ pump is the result of continuous improvements to the SP270 pump platform and has been qualified to comply with FDA and EMA requirements and has a Drug Master File (DMF).

Predefined doses are available in the standard SP270+ range, from 50 µL up to 140 µL. The preliminary bioequivalence study is performed with the closest pump engine to demonstrate that the average dose is consistent through container life.

In order to propose a customised packaging system that is as close as possible to the reference product, our

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Originator Product Qualification
Product description | Bill of materials | Dimensions

↓

Alternate Delivery System Identification
Dose | Spray | Raw materials | Look & feel

↓

Equivalence Verification: Preliminary Tests
Comparative study between Originator & Nemera delivery system

↓

Customised Device

↓

Nemera Delivery System Validation
Proven equivalence to the Originator

Figure 1: Device Equivalence Program process overview.

Figure 2: Nemera's standard platform for nasal sprays comprises the SP270+ pumps range and various nasal actuators.

> "We develop a customised dose via a dedicated pump engine to match a value within ±5% tolerance of nominal originator dose."

Device Equivalence Program relies upon the following four main parameters:

- **Dose**
- **Spray performance**
- **Raw materials**
- **Look and feel (design, priming, actuation force, etc).**

Then we develop a customised dose via a dedicated pump engine to match a value within ±5% tolerance of nominal originator dose. While dose adjustment is performed through pump engine fine-tuning, spray performance is accomplished through actuator re-design.

STRONG REGULATORY SUPPORT

Nemera has considered guidelines for the United States (FDA), Europe (EMA) and Brazil (ANVISA), regarding characterisation of nasal spray drug products and *in vitro* demonstration of pharmaceutical equivalence between two products:

✓ Draft Guidance for Industry-Bioavailability and Bioequivalence for Nasal Aerosols and Nasal Sprays for Local Action: FDA, April 2003

✓ Guideline on the Pharmaceutical Quality of Inhalation and Nasal Products: EMEA/CHMP/QWP/49313/2005 Corr.

✓ Guidance for Pharmaceutical Equivalence and the Bioequivalence of Nasal Sprays and Aerosols: ANVISA, July 2008.

The FDA draft guidance is the most detailed and stringent regulation compared with the approved European and Brazilian regulations. The US regulation encompasses the requirements of the other regulations although some differences in test procedure may be noticed. For common tests, the Brazilian regulation refers widely to the US regulation while the European guidance offers only a few indications. Therefore, our Device Equivalence Program is based

mainly upon the FDA guidance testing requirements, such as:

- Single actuation content (SAC) through container life
- Droplet size distribution (DSD)
- Spray pattern
- Plume geometry
- Priming and re-priming.

ROBUST STATISTICAL METHODOLOGY

The statistical analysis methodology used for each *in vitro* test to compare the equivalence of Test (T) and Reference (R) data tests and ultimately to conclude on the *in vitro* equivalence of the devices, is essentially based on guideline: "US/FDA Statistical Information from June 1999 Draft Guidance and Statistical Information for *in vitro* Bioequivalence Data", posted on August 18, 1999," which indicates:

- For the following tests (SAC, DSD [D50 and SPAN] & Spray Pattern), a bioequivalence criterion (geometric mean ratio T/R) and a bioequivalence limit (95% Upper Confidence Bound) should be calculated. This 95% value estimation is based on the assumption of normal distributions of the log-transformed data. If the result of bioequivalence limit calculation is negative, Reference and Test products are considered equivalent.
- For the plume geometry test, the bioequivalence criterion geometric mean ratio T/R after log-transformation is compared to the bioequivalence limit defined as point estimate: 90%-111%.
- For priming and re-priming tests, no statistical analysis is required.

Figures 3, 4 and 5 show example data from: a DSD test; plume geometry test; and a spray pattern test, respectively.

A RELIABLE & ROBUST SOLUTION

Nemera's Device Equivalence Program provides a high confidence level on results of the final product registration thanks to this preliminary bioequivalence study. Its objective is to propose a delivery system with comparable performance to the branded device in terms of design, patient usage and performance. The *in vitro* bioequivalence study can be performed with third-party formulations in our laboratory.

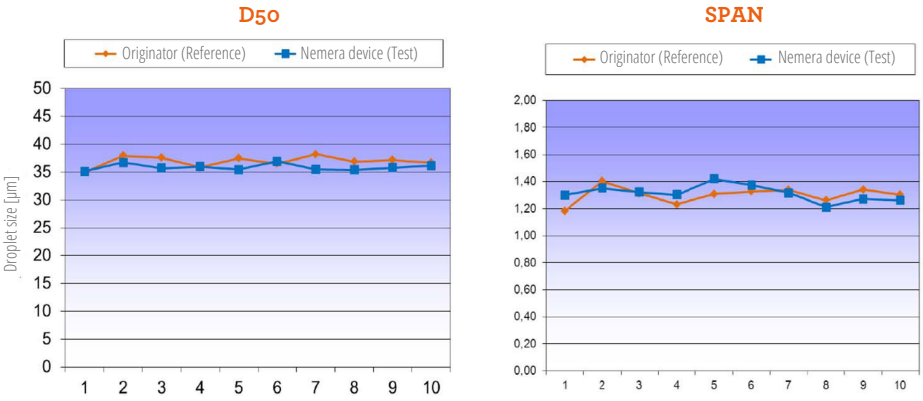

Figure 3: Examples of Droplet Size Distribution (DSD) test results data.

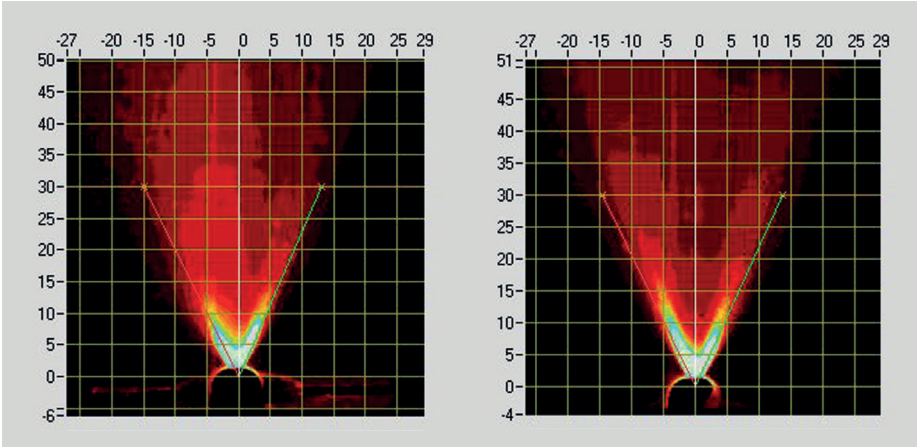

Figure 4: Example data from Plume Geometry (comparison of angle and shape of plume).

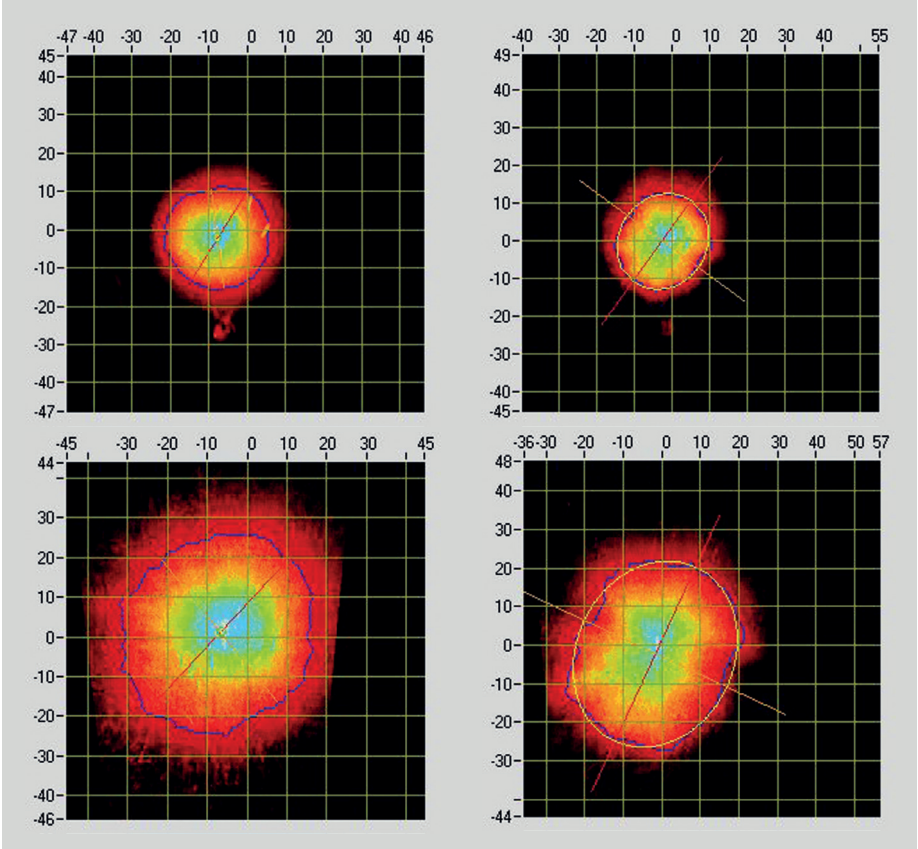

Figure 5: Data from Spray Pattern test at two distances from the actuator orifice.

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nasal/
buccal/
auricular

pulmonary

dermal/
transdermal

parenteral

ophthalmic

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