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.

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 programs.

**Bioequivalence for Nasal Sprays:**
Importance of Device Performance

Nemera Device Equivalence Program

- Preliminary bioequivalence study : derisking approach to speed-up project development
- High-level protocol and robust statistical approach based on the EMA and FDA guidelines
- Specific methodology to support “performance matching” activities in nasal sprays
- A cutting edge laboratory for device performance in-vitro testing support

**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 and Rexam delivery system

**Customized device**

**Nemera delivery system validation**
Proven equivalence to the Originator
Nemera's standard platform for nasal sprays is the SP270+ pumps range and various nasal actuators. The new optimized 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.

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

In order to propose a customized packaging system that is as close as possible to the Reference product, our Device Equivalence Program relies upon the following 4 main parameters:

• dose
• spray performance
• raw materials
• look and feel (design, priming, actuation force, etc.)

Then we develop a customized dose via a dedicated pump engine to match a value within ±5% tolerance of nominal originator dose.

While dose adjustment will be performed through pump engine fine-tuning, spray performance will be accomplished through actuator re-design.

**Strong regulatory support**

Nemera has considered guidelines for the United States (US-FDA), Europe (EU-EMA) and Brazil (Br-ANVISA), regarding characterization of nasal spray drug products and invitro demonstration of pharmaceutical equivalence between 2 products:

- ✔ 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 to 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 through container life (SAC)
- 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 to ultimately 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.”

- For the following tests (SAC, DSD [D50 and SPAN] and 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 under 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 as equivalent.
- For the plume geometry test, the bioequivalence criterion geometric mean ratio T/R after logtransformation is compared to the bioequivalence limit defined as point estimate: 90%-111%
- For priming and re-priming tests, no statistical analysis is required.

Data example

✔ Droplet Size Distribution (DSD)

D50

Originator (Reference) Nemera device (Test)

SPAN

Originator (Reference) Nemera device (Test)

✔ Plume Geometry: comparison of the angle and the shape of the plume

Originator (Reference) Nemera Device (Test)
✔ Measures on Spray Pattern at 2 distances from the actuator orifice

**Originator (Reference)**

3 cm

![Image 1](image1.png)

![Image 2](image2.png)

6 cm

![Image 3](image3.png)

![Image 4](image4.png)

**Nemera Device (Test)**

A reliable and robust solution

Nemera’s Device Equivalence Program will give you 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 characteristics. The in-vitro bioequivalence study can also be performed with your formulation in our laboratory.