



THE DEVELOPMENT PATH TO BIOEQUIVALENCE FOR A NASAL SPRAY

In this article Pascale Farjas, Global Category Manager, ENT Products, Alain Regard, Technology Product Manager, and Céline Petitcolas, Customer Technical Support, all of Nemera, discuss the steps taken when designing a nasal spray device for the growing bioequivalence market and the key competencies, including experience with regulations and regulatory agencies in numerous geographic regions, that Nemera can offer throughout the process.

An observation of generics in the nasal spray market will reveal to the keen observer an opportunity. Whilst the overall nasal spray market is currently experiencing limited growth, the market share of generics is increasing at a much faster rate. Seeing this, Nemera has established a unique approach for developing devices in this field. This approach follows seven steps:

1. Understand the market and identify the best reference nasal sprays to target.
2. Appraise the regulation and, by isolating the most stringent requirements, use it to drive the programme.
3. Establish the identity of the device (e.g. bill of materials, performance, patient use) using a supply of the reference from different markets.
4. Develop the device, based on Nemera's pump platform, to have equivalent performance to the reference device with the reference drug formulation.

5. Test the performance, comparing the Nemera device with the reference with iso-formulation in a comprehensive study, to demonstrate bioequivalence (Figure 1).
6. Prepare the "datapack" containing robust statistical analysis to be delivered to the client, the data therein being used simultaneously to support the drug registration process and justify the device selection.
7. Repeat the study with the final drug.

UNDERSTANDING THE MARKET

The topical nasal preparations market, as per the Anatomical Therapeutic Classification (ATC), is currently estimated at a value around US\$5 billion (£3.8 billion). Well over half of this market is for corticosteroids (Figure 2), due to the fact that they remain the frontline treatment for moderate to severe allergic rhinitis (AR) as the most effective option for relieving nasal

symptoms. The second thing to note is that the entire topical nasal formulations market is growing and evolving.

There are two key trends that can be observed as driving this evolution. First is increasing competition from generics. Nasonex (mometasone furoate), for example, has generic competitors with US FDA approval. Second is established brands shifting from a prescription-only to an over-the-counter (OTC)



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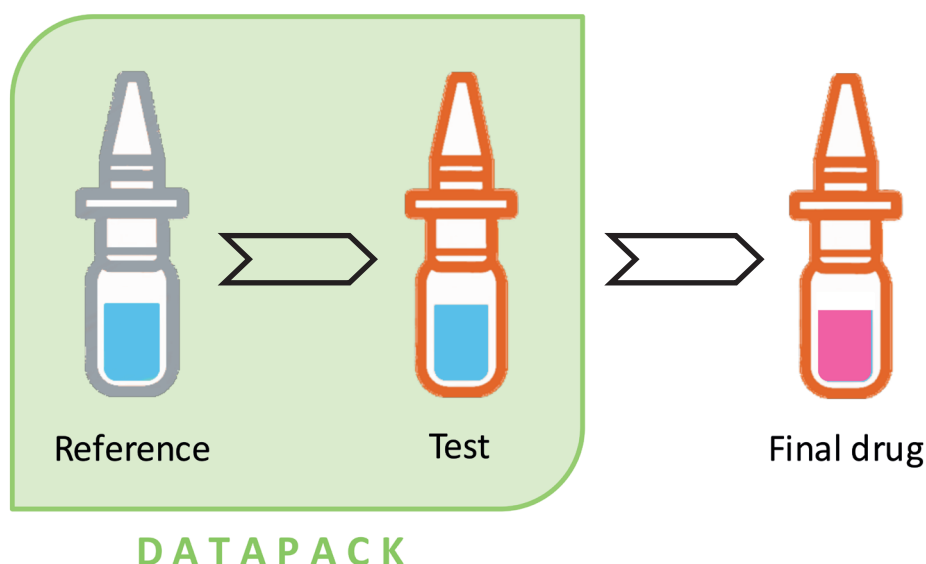


Figure 1: Nemera's device is compared to the reference with iso-formulation, in a comprehensive study to demonstrate bioequivalence, before testing with the final drug.

model, an example of this would be Sanofi's Nasacort AQ which was the first intranasal corticosteroid (ICS) in the US to make the switch, back in 2013.

Such trends are to be expected in a mature market and contribute to steady growth (1% CAGR in the period 2014-2016). However, with this observed increase in generics, the market share for generics increased from approximately \$1.4 billion in 2014 to \$1.7 billion in

2016, and improving access to healthcare, especially in developing countries, the future of this market looks to be both secure and promising. As such Nemera has selected a number of corticosteroids as part of their bioequivalence programme.

APPRAISING THE REGULATION

When looking at ICS as a global market it is important not to underestimate the

complexity of the regulatory landscape. Across the world there are several co-existing regulatory ecosystems, each with a different approach to bioequivalence. The most frequently mentioned is the US FDA, often considered to have the most stringent regulation. The FDA issues precise guidances for bioequivalence and statistical approaches. Additionally, they have drug specific guidances for generic products submitted under an ANDA. When assembling the datapack further down the development pathway Nemera uses its understanding of the regulatory environment to tailor the strategy to the target geographic market.

Looking elsewhere, EU regulation has the nuance that each member country may have a different interpretation of the regulations and directives. In the EU, for ICS, there are generally more submissions for hybrids than generics.

Of course, differences are far more noticeable when moving to emerging markets such as China. One of the hurdles that must be leapt when getting a drug approved for the Chinese market is finding a suitable agent to assist in the filing process. Not only will an application to the CFDA need to be translated but, if the application is filed by a foreign company without a Chinese office, an agent is also a legal requirement, similar to how an agent is required as an intermediary when dealing with ANVISA in Brazil. It is also worth noting that the CFDA has, at present, no clear guidance on liquid dosage for bioequivalence. Whilst the aim seems to be to synchronise with the US FDA, CFDA regulation is still very much under construction.

As Nemera focuses on the most stringent regulation during development, here we shall use the FDA as the exemplar for how Nemera supports the registration process. Under FDA guidelines, whatever the regulatory position of the targeted reference product (i.e. prescription only or OTC not under monograph), a generic product will follow the same process for its first submission and must therefore answer to the same requirements. When modifying the dossier, that is to say when making a variation upon the first submission (e.g. to add a second source), there are two ways to go about it. The first is to repeat the same process as the first submission and the second is to use a simple equivalence of performances of the pumps, thereby bypassing the need to follow the full guidance on bioequivalence for generics.

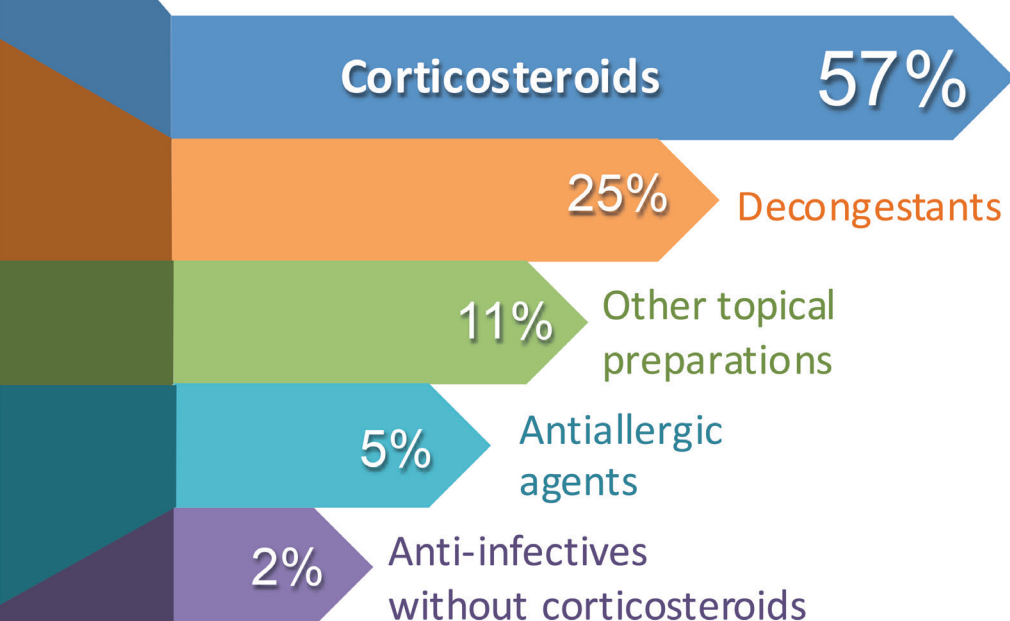


Figure 2: Worldwide intranasal market by drug type. (Source: IMS Health)

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When going through the process of registering a generic however, it may be more relevant for authorities to compare the variation directly to the reference product. A suitable analogy would be to imagine a simple door key: a copy of the master key would most likely be able to open its door, but a copy of a copy is less likely, and increasingly so the further down that rabbit hole you go. It's important to copy a key directly from the master and, likewise, it is important to test bioequivalence directly from the original reference product. Thanks to its deep experience with these processes, Nemera can strongly support a submission document with the chapters linked to the device.

ESTABLISH THE IDENTITY

In simple terms, a nasal spray is the combination of two regulated products, a drug and a device, which together make the combination product. Nemera's expertise is in the latter of these two, the spray device, but it remains crucial to acknowledge throughout the design process that the device is part of the greater combination product. The device is a major contributor to treatment efficacy, patient safety and robustness of the combination product. Nemera takes steps to ensure that the critical factor of device performance is under control at all stages of development.

A spray device has three main functions:

- Preserving drug product integrity
- Delivering an exact preset dose
- Delivering drug product to the targeted site.

In more detail, when discussing product integrity the main things to consider are ensuring that the device does not leak, that there is no weight loss (indicating an evaporation of solvent and therefore a change in the potency of the drug product) and that the extractables and leachables

profiles of the device materials are within regulatory limits. On the last point, Nemera performs studies to determine these profiles for the toxicological assessment and carefully selects the raw materials for the device.

The second two functions are both aspects of delivery. A preset dose of the API translates, at the device level, to a consistent weight of shot throughout the product's lifespan. Whilst a critical aspect of both efficacy and safety, it is perhaps the easiest of the three functions to control. The third function, delivering drug product to the nasal cavity in a consistent manner, requires consistent spray characteristics. Nasal sprays are characterised by droplet size distribution on the one hand, and spray geometry (a combination of spray pattern and plume geometry) on the other. These attributes contribute to the deposition pattern inside the nasal cavity and therefore play a role in the efficacy of the final combination product.

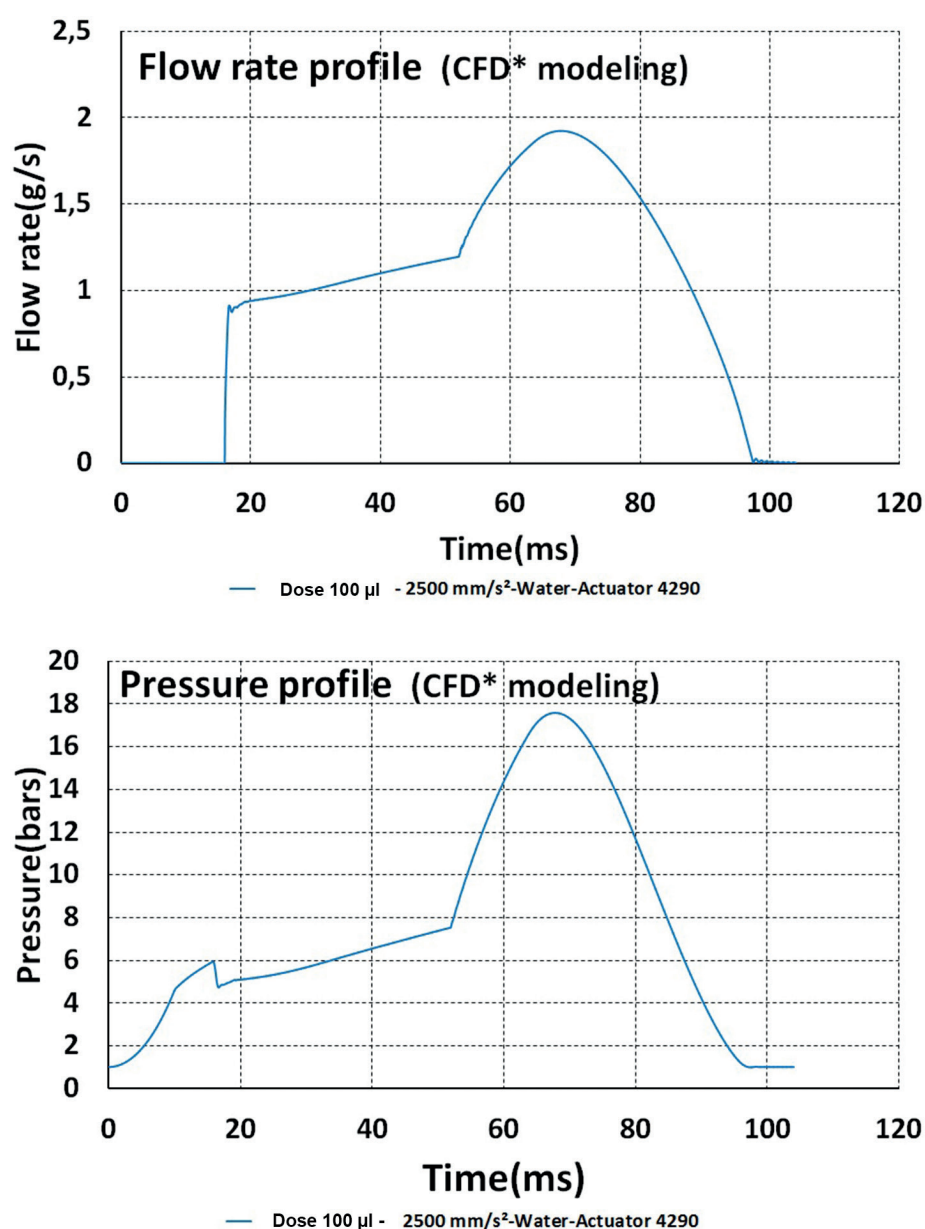


Figure 3: Flow rate profile (top) and pressure profile (bottom) from numerical modelling of a Nemera pump.

DEVELOP THE DEVICE

The discussion of device identity invariably brings us to the spray, which in point of fact is the hardest aspect to control, thus it is spray generation where the greatest effort must be expended during development of the device. With this in mind, let's turn to the heart of a nasal spray device: the pump. The pump has multiple functions, one previously touched upon is metering, ensuring the delivery of a preset dose.

Another primary function of the pump is to generate a flow and, furthermore, control flow rate and pressure level to master the generation of the spray. The flow rate and pressure profiles are dependent upon the pump technology and the actuation profile, with the nominal dose of the pump also having influence due to its impact on spray duration.

Figure 3 shows the outputs of numerical modelling of one of Nemera's pumps. The pump modelled had a dose of 100 μL , the test fluid was water and the nozzle was also a design of Nemera's. The flow rate profile shows that the dose is dispensed in under 100 ms with a flow rate of 1-2 g/s. In conjunction, the pressure profile shows that this flow rate generates an internal pressure rising to 18 bar. Such models are important to understand the physical behaviour of the pump fully, which in turn permits the prediction of outputs from the pump for given inputs.

Moving from heart to head, the next key part of the device to focus on in development is the nozzle (Figure 4), which is surprisingly

complex. Inside a nozzle tip are several vertical channels which then enter into convergent channels to move the rising liquid into a swirl chamber before exiting through the orifice at the tip of the nozzle. It is noteworthy how small the dimensions of all these parts are, typically in the range of 0.2-0.4 mm, especially given the complex geometry. As such, high precision manufacturing is required to ensure that the final combination product generates a consistent spray after scale-up to industrial manufacture.

Of the nozzle's components, the swirl chamber is perhaps the most interesting. Figure 5, a velocity profile of the fluid as it passes through the nozzle, clearly shows the swirl motion. In the swirl chamber at the centre, the fluid can be seen rotating and converging to the spray hole. The combination of the rotational and axial speeds generates an overall speed profile at the orifice that forms a rotating cone. The flow rate used in this simulation is 1.2 g/s, which is on the lower end of the flow rates for this pump, as seen previously. It is worth pointing out the magnitude of the fluid's velocity at the orifice: 48 m/s. For comparison, this is equivalent to 170 km/h or 105 mph, and the value nearly doubles when the flow rate reaches maximum.

When a fluid leaves a narrow orifice at such speed it breaks up into droplets in the first 2 mm after exit

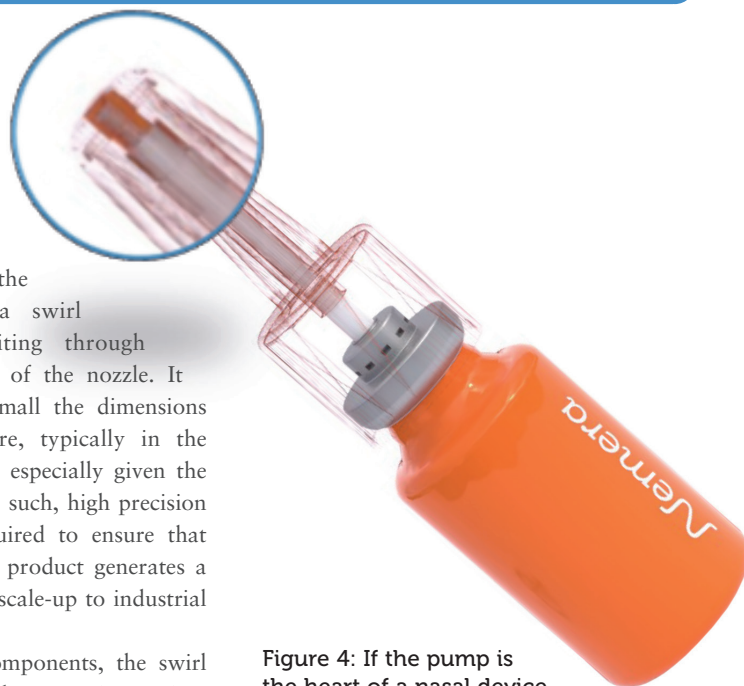


Figure 4: If the pump is the heart of a nasal device, then the nozzle is its head.

(Figure 6, see next page). These droplets form the basis for analysing how well and how consistently the device will deliver drug product inside the nasal cavity. These droplets, and hence the spray, are hugely impacted by the viscosity, and to a slightly lesser extent the surface tension, of the drug formulation. Batch-to-batch variability of viscosity can be significant and must be taken into account when designing a spray with a defined target as is the case in the bioequivalence approach. Because the impact of viscosity is so tremendous, the factors that affect viscosity, such as temperature, the delay between actuations and the fluid memory effect (i.e. whether or not the product has been shaken), must in turn be considered.

Velocity Magnitude

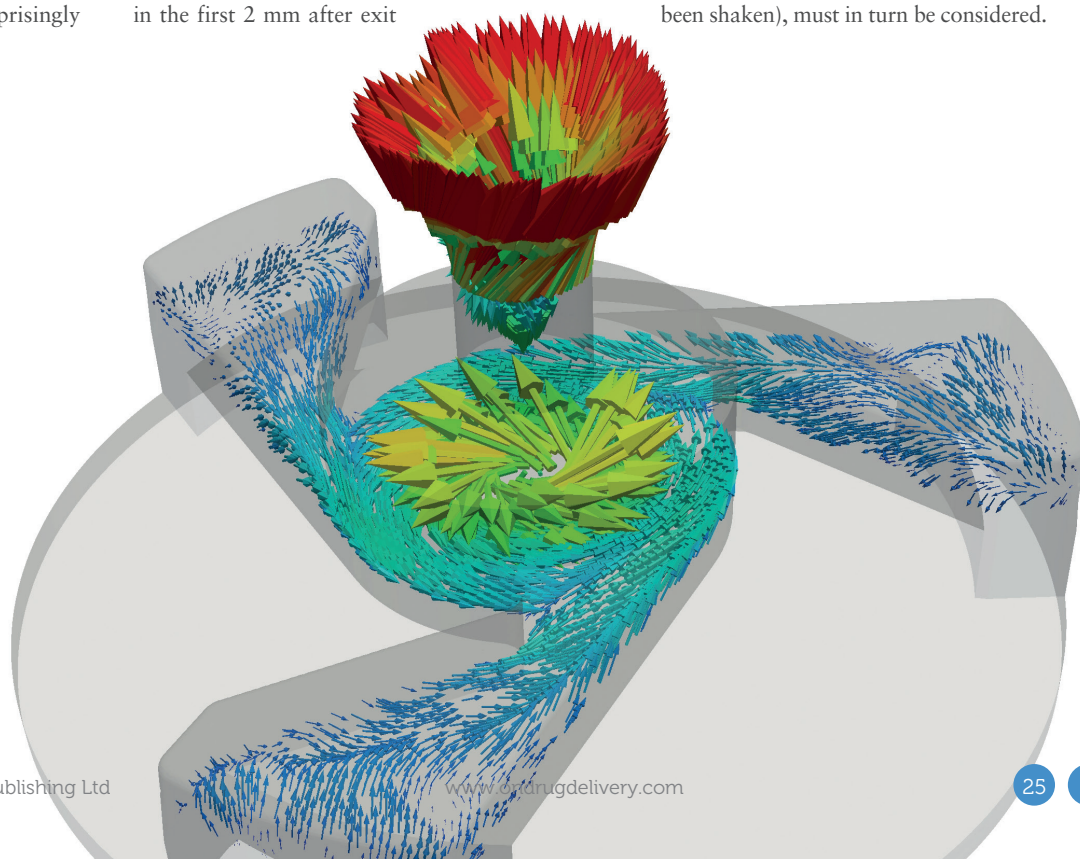
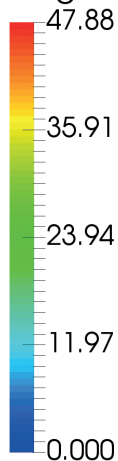


Figure 5: Velocity profile of fluid passing through the nozzle, showing the swirl motion.

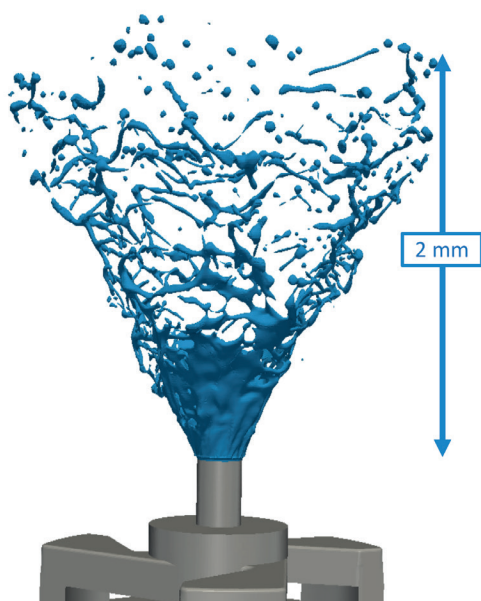


Figure 6: CFD representation of fluid break-up as it exits a nasal device.

Nemera approaches this complex development process with multiple tools:

- Experimental testing and a database of results helps track input and performance data as well as aiding in the analysis of influencing factors and trends.
- The capacity to manufacture fully functional, novel nozzles in a matter of weeks, including metrology control, enables the exploration of the design space and shorter tuning loops.
- Computational fluid dynamics (CFD) modelling allows for a richer understanding of the physics involved. CFD can also be used to run sensitivity analysis on specific parameters, as seen earlier in this article.
- Finally, mathematical modelling makes the link between input variables and output performance.

Understanding the sensitivity of the performance in the design space allows the set-up of control strategies, ensuring robust and controlled performance when it comes to mass production. And, by incorporating data analysis and mathematical modelling into development, Nemera achieves acute refinement of the design, all building to one ultimate goal: to have the spray on target.

TESTING THE PERFORMANCE

Nemera has developed its own testing laboratory using cutting-edge technology. Customised testing methods are used to cover all aspects of a nasal device from broad parameters (dosage accuracy, leakage, weight loss, etc) to in-depth spray characterisation. Tests are also performed on the component materials to establish extractables profiles. All of which can be customised to the needs of clients and partners.

Of the tests performed one of the most interesting is spray characterisation. These tests are very sensitive and use advanced, automated equipment to perform three analyses:

- Droplet size distribution, testing the size of droplets in a spray

- Spray pattern, a horizontal cross-section of the spray to show spray area, shape and homogeneity
- Plume geometry, a vertical cross-section of the spray to estimate spray angle and width.

All of these tests can be influenced by a litany of factors, either from the environment (enclosure, lighting, calibration, manual/automatic priming, device setting, input parameters, etc) to the sample itself (shaking, temperature, alignment, etc). On top of that the selection of data for analysis is a huge part of the final result as well. In order to ensure the reproducibility and reliability of the data, measurements are taken when the spray has fully developed during its stabilisation phase, somewhere between 30 ms and 180 ms (Figure 7).

PREPARING THE DATAPACK

As previously mentioned, after testing a device with the reference product, Nemera prepares a datapack containing statistical analysis of the tests. The purpose of this is to maximise the chance of a successful application for bioequivalence across geographic regions and, as such,

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PBE is a more complex calculation than ABE, but guidance is available with detailed formal framework, whereas there is none for ABE. Nemera offers experience and expertise in both systems to assist partners and clients through these bioequivalence *in vitro* tests.”

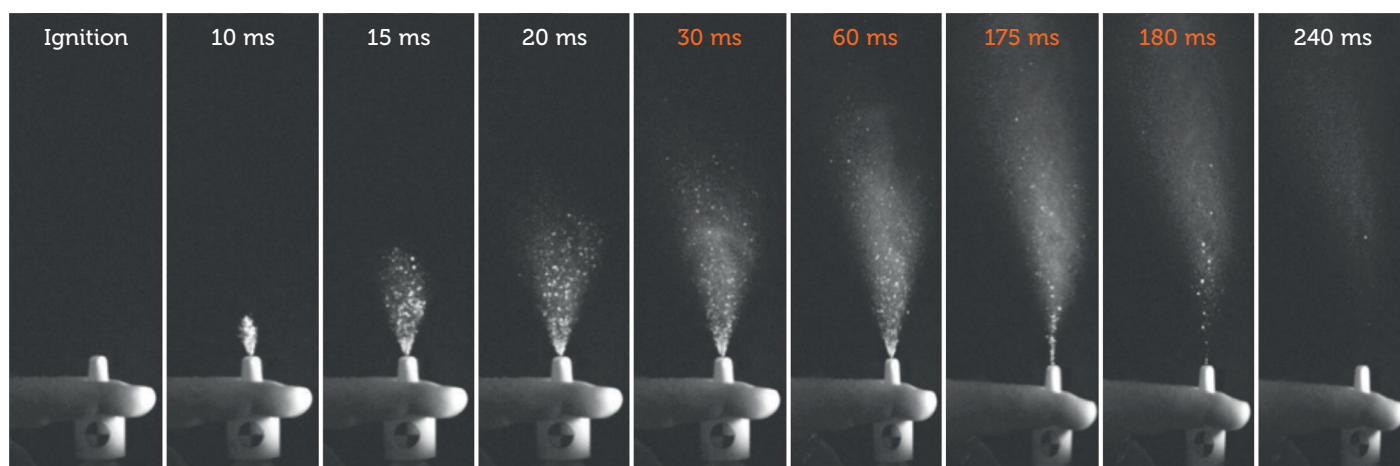


Figure 7: The stabilisation phase of a spray occurs between 30 ms and 180 ms.

highlights the main differences between regulators. One such difference is in the calculations required in the US (and those that base their regulation on FDA guidelines) and Europe. The US prefers Population Bioequivalence (PBE) and Europe prefers Average Bioequivalence

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CONCLUSION

Nemera brings great benefits to partners looking to develop a generic nasal spray, a process far more complex and involved than it may first appear, but which growing market demand worldwide shows is increasingly likely to be a worthwhile endeavour. Able to offer expertise in market understanding, regulatory affairs, device development and statistical analysis, Nemera also prides itself on being a co-operative, committed and responsive device design partner.

ABOUT THE COMPANY

Nemera is a world leader in the design, development and manufacture 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)
- Inhalation (pMDIs, DPIs)
- Parenteral (auto-injectors, pens, safety devices & implanters)
- Ophthalmic (multi-dose, preservative-free eyedroppers)
- Dermal and transdermal (airless & atmospheric dispensers).

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.

ABOUT THE AUTHORS

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 Centre for Devices (ICD), leads the nasal and dermal developments. He drives some Nemera own IP projects as well as working on several customer product developments in the field of nasal and dermal applications.

Céline Petitcolas holds a Materials Engineering degree from the École Nationale Supérieure de Chimie et de Physique in Bordeaux, France. Her current position is Customer Technical Support for nasal range at Nemera. Following a first R&D experience in the automotive industry, Céline joined Nemera in 2012 to develop pharmaceutical devices, focusing especially on the nasal spray area. Her new role consists in helping and assisting customers from a technical point of view in their development of nasal sprays and more specifically in the area of bioequivalence. Ms Petitcolas is the preferred technical contact for customers as she interfaces with multiple Nemera teams (marketing, sales, technical) to bring customers and partners the support they need.



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