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In vitro nasal spray characterization

When to perform spray characterization tests in the development cycle of a nasal spray product

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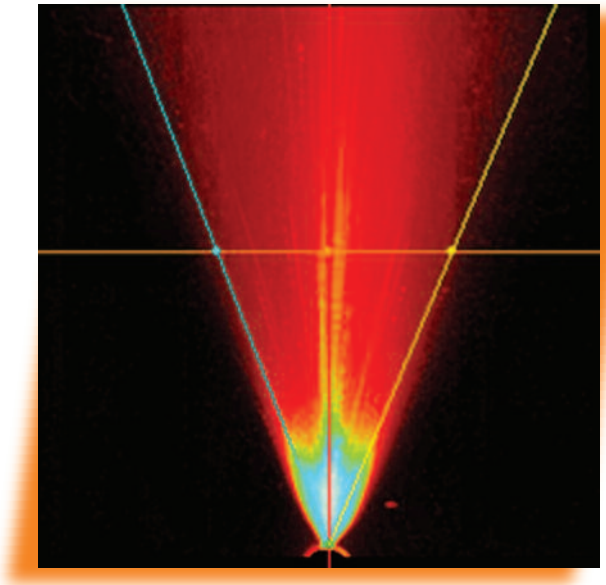

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Due to the complex nature of nasal spray products whose performance depends on an interaction between the formulation and the delivery device, analytical requirements for the approval of nasally administered drugs greatly exceed those for solid dosage forms. While the relationship between certain spray characteristics and the therapeutic effect of a product is still under investigation, the FDA currently requires numerous techniques for characterizing nasal spray drug products for New Drug Applications (NDAs) (Table 1) [1]. Submissions of Abbreviated New Drug Applications (ANDAs) also require a subset of these tests to demonstrate *in vitro* bioequivalence for locally acting nasal sprays per the FDA draft bioequivalence guidance [2].

These analyses can require significant investments in time and labor, so you want to get the most out of them. In order to maximize the benefits, it is important to develop an understanding of the optimum timing of spray characterization studies, especially if you are new to nasal spray product development.

Table 1

FDA Chemistry, Manufacturing, & Controls (CMC) analytical techniques and drug product characterization studies for nasal sprays and nasal aerosols

Physical/Chemical	Spray/Device Characterization
Appearance	Pump delivery
Identification	Spray content uniformity
Assay	Droplet size distribution
Net content	Spray pattern
Impurities and degradation products	Plume geometry
Preservative content (if present)	Weight loss (on stability)
Particulate matter	Extractables/leachables
Microbial limits	Particle size distribution by
pH	cascade impaction (nasal aerosols)
Osmolality	Prime/reprime
Viscosity	Profiling (tail off)
Particle size distribution (suspended drug substance)	*In vitro* dose proportionality
	Effect of dosing orientation

Your regulatory strategy will also depend on where you decide to seek approval. For example, Health Canada and EMEA [3, 4] do not require spray pattern and plume geometry analyses (Table 2) for release testing and drug product characterization, while Brazil has issued a new draft guidance on bioequivalence for locally acting nasal sprays. In addition, specifications on pump delivery, spray content uniformity, and droplet size distribution vary between regulatory bodies.

Table 2

Variations in Regulatory Requirements from FDA, Health Canada (HC) and EMEA

Metric/study	FDA	HC/EMEA
Spray pattern	X	
Plume geometry	X	
Droplet size distribution	X	X
Physical characterization*		X
In vitro dose proportionality	X	

**Development phase. Consider evaluating highly functional excipients throughout development and stability.*

However, even if you do not initially plan to market the product in certain countries, for example, the United States, you might still consider performing the spray characterization tests necessary to meet the requirements of the relevant agencies. If you do not conduct spray pattern and plume geometry tests because you are filing only in Europe, and then later decide to market the product in the US, you might need to do additional stability testing and will definitely need to spend a good deal of time and money to develop methods and specifications at that point. In those types of cases, doing all of the tests at the earlier stage would be more efficient and more cost effective.

Although the FDA requires *in vitro* spray characterization studies such as droplet size and spray pattern for approval, the same methods used to support stability, batch release, and drug product characterization for NDAs and ANDAs can also serve in a supportive role throughout a nasal spray's development cycle. Beginning these analyses at appropriate times throughout the development can establish reproducible spray performance to ensure that clinical trials produce the most reliable results possible and to head off avoidable formulation and device performance problems from the start.

Development and pre-IND

As the nasal spray drug product begins to take shape, you should take both formulation and device attributes into consideration in order to ensure that the two aspects of the product work together. If testing reveals that the selected delivery device does not produce a consistent spray or the desired droplet size with your formulation, it is much more cost effective to make changes at this point then after clinical studies have been completed. In addition, you can use the results as supplemental data to support an Investigational New Drug Application (IND).

Early spray characterization studies add value to final selection of both device components and the concentration of excipients because formulation viscosity and the magnitude of droplet size and plume angle correlate [5], and surface tension may impact droplet size results [6]. For example, a particularly viscous formulation might not produce expected results with a pump whose characteristics were determined using water, requiring changes to either the device or the product. Or analysis may reveal that a lower viscosity formulation in conjunction with a particular device results in a more desirable droplet size, which might lead to the selection of a different grade, or a different concentration, of a polymer such as carboxymethylcellulose.

Once the formulation and device selection have been finalized, it is a good idea to determine the product's spray characteristics prior to the start of clinical studies. Clinical trials have enough inherent variables associated with them; the last thing you want is to introduce more uncertainty, particularly speculation about whether or not the patient actually received a dose if the unit failed to prime per your expectations. Even though the determination of the final packaging such as selection of the bottle and the labeled number of doses may not take place until later in the development process, conducting these tests early on allows you to provide clinicians and volunteers with appropriate instructions for use.

Often overlooked parameters that might prove useful at this stage include:

- Priming
- Re-priming
- Number of metered doses
- Dosing orientation (head tilted backward, forward or held straight)

In particular, for a viscous formulations that might produce significantly different spray characteristics than water in particular pumps, confirming the number of priming sprays required before a trial can prevent doubts about the validity of clinical data.

Other questions to answer at this point might include:

- How many days can the unit go unused before it requires priming?

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- How many repriming sprays are required?
- For a multi-dose drug product used in dose escalation studies, do you have enough fill volume to deliver full doses with every spray?
- Will patients need to tip their heads back to avoid having a solution drip out of the nose?

Recently, the FDA has requested that sponsors submit additional CMC data with the Investigational Drug Application (IND), and spray performance measurements can provide some of that data. Spray characterization data appropriate for this stage might include any or all of the following:

- Pump delivery (PD)
- Spray content uniformity (SCU)
- Droplet size distribution
- Spray pattern
- Plume geometry.

In the case of a solution formulation, pump delivery (PD) may serve as a surrogate for spray content uniformity (SCU) to conserve resources at this phase of development since PD takes less time than SCU. However, confirming first that the correlation between the PD and SCU exists is prudent. Suspension formulations always require SCU because the spray weights measured by PD cannot verify the homogeneous distribution of API.

During clinical studies

Method validation. As the nasal spray drug product advances through Phase II clinical trials, consider transitioning all working test methods into validated test methods. At the latest, validation of all methods should take place before registration stability begins. The FDA sets specifications for spray content uniformity, for example, but you must set specifications for droplet size and spray pattern yourself. The rigorous data collection necessary to develop your own specifications for spray characterization methods requires a minimum of several months, so you should begin as early as possible.

The FDA's guidance for this process, titled "ICH Q2B validation of analytical procedures: Methodology," sets out guidelines that may not prove relevant for some spray characterization tests. For example, the guidance specifies linearity as a necessary feature, but droplet size and spray pattern rarely correlate linearly with concentration of the drug product unless viscosity changes with API concentration. In addition, the lack of reference standards for tests like plume geometry, droplet size, and spray pattern can make accuracy and specificity difficult to establish. As a result, a validation approach for spray characterization studies will typically focus on repeatability, intermediate precisions, and robustness, an approach that can require a substantial amount of time.

You do not want to rush through setting specifications for the tests without acquiring sufficient data because setting the specs too narrow can result in later testing failures, and regulatory bodies may challenge specifications set too wide. Testing multiple batches if they are available during this period, and conducting an R&D stability study, will give you an early read on the physical and chemical stability of the drug product and provide you with adequate data to set specifications.

Extractables and leachables. It is a good idea to begin extractables studies during Phase II if at all possible. If the extractable profile reveals entities above the analytical evaluation threshold (AET) that require monitoring, you will need to monitor those during a leachable study. For practical and financial reasons, the leachable study should take place concurrently with your registration stability batches because you can store units for both studies at the same time under the same conditions. In order to have sufficient planning time for the leachable study, you will need to complete the extractable profile and evaluate any compounds of concern as far ahead of the scheduled start of the registration stability study as possible.

Registration stability and product characterization. The FDA requires testing of 3 registration batches prior to submission of an NDA. In addition to analysis of physical characteristics and microbiological testing over the course of the stability study, most sponsors also choose to include spray pattern, although spray pattern and plume geometry are not required. These registration stability study designs (Table 3) typically involve the analysis of over 10,000 units over a 2-3 year period. As a result, poor planning, such as failing to place a sufficient number of units in the stability chambers, can delay filing with regulatory bodies.

Drug product characterization studies on samples from the three registration batches should also take place along with regulation stability. One-time drug product characterization studies performed at this stage include, where appropriate:

- Photostability
- Temperature cycling
- Device robustness
- Profiling
- Effect of dosing orientation
- Prime/reprime
- Cascade impaction for nasal sprays to determine the percentage of droplets less than 10 μm.

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Table 3

Example of a stability study design for a multi-dose nasal spray suspension drug product with preservatives. Other formats and design options may be appropriate for given drug products or regulatory strategies.

Storage Condition	Time (months) 1	3	6	9	12	18	24
25°C/60%RH	NT	A	A, B, C	A	A, B, C	A	A, B, C, D
40°C/75%RH	A	A	A, B, C, D	NT	NT	NT	NT
30°C/65%RH	E	E	E	E	E	NT	NT

NT = Not Tested
A = Appearance, Assay, pH, Viscosity, Weight Loss, Degradation and Impurities, Preservative Content, SCU, PD, Droplet Size, Particulate Matter, Particle Size (API), Spray Pattern.
B = Microbiological testing
C = Preservative effectiveness
D = Leachables
E = Reserve samples tested in the event of a failure during 40°C/75% RH.

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