Meeting expectations for FDA nasal spray Q3 structural equivalence

A new weight of evidence approach may allow regulatory approval based on *in vitro* testing alone

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Introduction

Access to affordable prescription medication continues to advance research for new approaches in generic drug product development. Generic applications are approved with an understanding that the dosage form has the same rate and extent of absorption as the innovator product and meets qualitative and quantitative (Q1/Q2) expectations. For complex dosage forms, establishing bioequivalence based on pharmacokinetic (PK) and clinical endpoint studies is challenging, given systemic drug concentrations may not correlate with local therapeutic response. The United States Food and Drug Administration's (FDA's) Generic Drug User Fee Amendments (GDUFA) initiatives support advancing regulatory science to determine equivalence of complex and locally acting topical dosage forms. These activities lend themselves to a new weight of evidence approach for ophthalmic, topical cream and ointment, inhalation and nasal spray drug products in that they may allow approval based on *in vitro* testing alone through the concept of Q3 structural equivalence (Table 1).

Table 1

New bioequivalence paradigm for complex dosage forms

Bioequivalence Weight of Evidence Criterion	Measure
Formulation/Device	Q1: Same components Q2: Same components in same concentration
In Vitro Similarity	Drug-product-specific guideline *in vitro* tests Q3: Same components in same concentration with the same arrangement of matter (microstructure)
Safety	Pharmacokinetic study
Efficacy	Clinical endpoint study

Q3 activities have led to collaborations between the FDA and scientists to develop new pathways for generic drug approval, resulting in growth of drug-specific guidelines for complex dosage forms.[1] In fact, Q3 equivalence concepts have already been successfully implemented through the approval of mometasone furoate nasal spray in 2016.[2] While this application involved a number of hurdles, approval was based on a decision to waive a clinical endpoint study for bioequivalence via a validated Raman spectroscopy technique for objective particle size analysis of mometasone.[2]

The role of Q3 equivalence

To illustrate the idea of Q3 structural equivalence for a nasal spray suspension (Figure 1), imagine that two products must possess similar viscoelastic behavior and spatial arrangement of the active pharmaceutical ingredient (API) and excipients, which produce drug-laden droplets that deposit in similar regions in the nasal cavity. Once deposited, the droplets spread similarly on the surface allowing the API to dissolve at the same rate and achieve similar permeation through the mucus into epithelial cells. Yet even this description oversimplifies the number of variables to be considered (Table 2).

Principles surrounding Q3 equivalence, however, are not new concepts; the pharmaceutical industry has been using these measures as part of the development cycle for numerous years. For example, quality by design (QbD) drives an understanding of critical quality attributes (CQA) and is utilized to identify the design space around the API, excipients and manufacturing steps.[3] Similarly, a Q3 mindset drives one to ensure that the dosage form particle/excipient interactions are not impacted by different process parameters and physicochemical stability is maintained.

Formulation and deformulation approaches point towards methodology to determine the signature of an API and/or excipient via particle size, particle shape and surface chemistry. The extent of agglomeration or association of the API with an excipient may impact the rate of dissolution thus impacting clinical outcomes. In addi-

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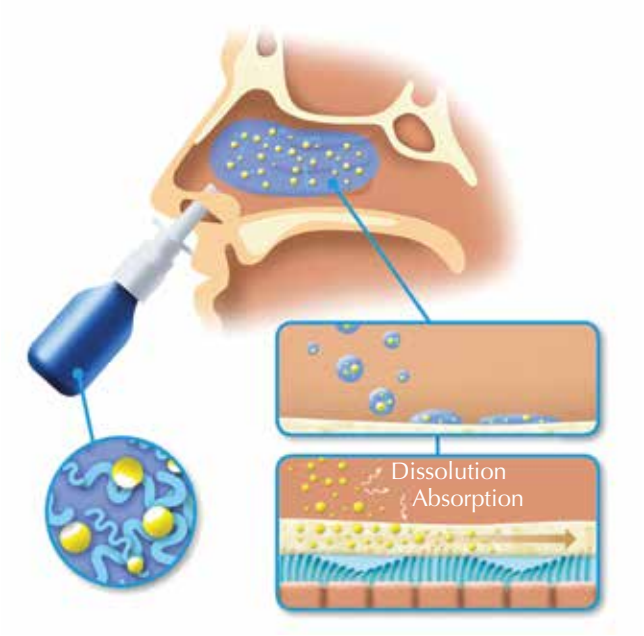
Figure 1

Envisioning the impact of structural performance of a nasal spray suspension: Drug particles of various sizes, shown in yellow, are distributed in a gel-like structure. The gel must enable stability of the formulation and also allow the product to be sprayed into the nasal cavity. Once deposited, the gel and embedded particles will spread on the mucus layer. The gelling nature of the polymers in the gel may impact the rate of dissolution and mucociliary clearance of the drug particles.



tion, polymorph screening may be relevant to ensure the crystal lattice formation between two APIs, for example, results in similar stability and bioavailability.[4]

Using these Q3 principles not only aids in development, but also helps de-risk expensive and timely clinic studies. How many of us have heard of or experienced a failed PK study because the particle size for one drug product was smaller compared to the other? Or that the device altered the aerosolization properties, resulting in a decrease in drug deposition? At a minimum, understanding the drug product microstructure may prevent failures in the clinic.

Q3 methodology—a work in process

Reducing structural equivalence to proven methods is a work in progress and, as noted above, drives much the FDA-funded research today. Ingredient-specific particle size approaches that rely on a chemical signature of the compound have been the most successful Q3 metric to date. Raman spectroscopy coupled with means to differentiate single particles from agglomerates result in particle size determinations from a statistically significant sample size.[5,6] Raman-based methods continue to improve and become faster, making this technique approachable for bioequivalence studies. However, Raman spectroscopy is not suited to measure particles smaller than 2 µm. New techniques are needed, such as automated scanning electron microscopy (SEM)[6] to include the sub-2 µm range.

Table 2

Defining Q3 parameters

Potential Q3 Attribute	Measures
Formulation and Manufacturing Processes	Particle size Particle shape Polymorphs Surface chemistry Adhesive/Cohesive forces Rheology Spatial arrangement Sedimentation Aggregation Stability
Patient and Delivery Device	Angle of insertion Inhalation rate Instructions for use Disease state Patient-to-patient variability Rheology Spreadability Droplet velocity Droplet size Particle size Aggregation
Dissolution and Permeation	Release rate Particle size Aggregation Electrostatics Mucoadhesion Lipophilicity
Clinical Outcome and Pharmacokinetics/ Pharmacodynamics	Modeling CFD Nasal casts Deposition pattern

Particle shape may also impact the rate of dissolution. Therefore, shape could play a role in achieving structure equivalence. In a study that compared dry powder formulations designed to match a Reference Drug Product (RLD), differences were shown in the particle size, depending how the particle diameter was calculated (Figure 2).[7] Particle size was measured using automated SEM from drug deposited on stage 4 of a Next Generation Impactor. It can be assumed that the particles all achieved the same aerodynamic particle size. The measured Dv50, reported using the average diameter, indicated similar particle size among all four formulations tested. However, the aspect ratio (the ratio of perpendicular to longest chord) indicated potential differences in particle shape and a lack of similarity for two formulations compared to the RLD. Understanding how particle size and shape are calculated is therefore an important consideration.

Applying Q3 principles to develop nasal products

Many nasal spray suspensions are Newtonian, such that the viscosity decreases with shear or agitation. This

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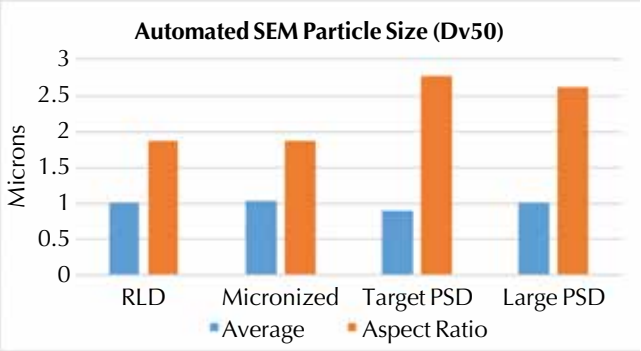
Figure 2

Particle size measured from dry powder inhaler formulations. Three formulations were manufactured by different processes to match the RLD formulation.[7]



shear-thinning behavior is necessary to break up the gel-like structure in the device container and allow the formulation to be sprayed. It has been demonstrated that viscosity influences not only the emitted droplet size but also the size of the spray/spray area.[8] The addition of polymers also aids in suspension of the API and stability of the drug product. In the concept of Q3 equivalence, it is easy to envision how the gel-like structure and rheological properties of a nasal spray are relevant.

Given the complex interaction of these thixotropic suspensions and the delivery system, traditional viscosity measurements may not be sufficient to understand equivalence between formulations. Techniques such as high shear rotational or capillary rheometry[5, 8] may be utilized to evaluate the higher shear forces that occur during actuation of the device and allow assessment of the viscoelastic behavior in terms of elastic behavior and fluid mechanics of each formulation. This represents a new area of research for nasal sprays.

It has been shown that dissolution is a rate-limiting step for absorption of nasal suspensions, particularly for low solubility corticosteroids.[9] At a recent FDA workshop in January 2018,[10] predictive dissolution methods for both inhalation and nasal spray drug products were presented and debated. Dissolution and permeation techniques include, but are not limited to, USP methodology, Franz cell diffusion, Transwell-based dissolution and cell-line-based transport studies.

Within each of these dissolution techniques, the number of variables ranges from using sink versus non-sink conditions to the manner of collection of the dose on the filter or cell surface. While it is generally agreed that a surfactant should be present in the dissolution media, the discussion continues on the type and concentration to be used. The rate of stirring is also part of the dialogue. Compared to the lung, nasal dissolution studies may be more challenging as the volume of mucus is much lower, which creates more difficulty in achieving sink conditions. Despite the ongoing conversation around the "how to," there is strong belief that dissolution methods could be a key link to predicting *in vivo* outcomes.

Link to the patient

Anatomical models may also represent a step towards understanding the impact of Q3 equivalence. Given that the site of deposition in the nasal cavity is linked to therapeutic outcomes, nasal casts may be a useful tool for comparison between two products. In fact, deposition patterns quantified in a nasal cast were utilized in an approval of mometasone furoate nasal spray by the European Medicines Agency (EMA).[11] Using realistic nasal casts, the influence of parameters discussed above, such as viscosity and spreadability, can be assessed. Patient use factors such as head orientation and timing of nasal inhalation during actuation can also be compared using nasal casts.[12] It is important to note that best practices include validation of the nasal cast model prior to its application as a decision-making tool. In addition, one may consider quantifying dripping (which is also a clearance mechanism) of the formulation from the nostrils or into the pharynx when building these models.

Other research is using information derived from spray characteristics, nasal casts and computational fluid dynamic modeling (CFD) to create a link to pharmacokinetic profiles or bioavailability.[13, 14] Formulation and particle size characteristics are coupled with patient factors such as angle of insertion in order to model deposition pattern in the nose. From there, theoretical assumptions on particle dissolution, diffusion, metabolism absorption and clearance from the nasal surface are made to quantify absorption in the plasma for PK modeling. Predictive PK may be the answer to eliminating aspects of *in vivo* studies in the future.[15]

For example, Longest, et al. have demonstrated a direct relationship between maximum plasma concentration (C_{max}) and middle nasal passage deposition.[13] If two formulations demonstrate similar Q3 parameters and sites of deposition, then conclusions about bioavailability could be made. Additional models have chosen to evaluate other regions of deposition as well as sub-compartments of the nasal surface (mucus layer, epithelium and submucosa).

It goes without saying that physiologic PK models are in their infancy and agreement on the input parameters much be achieved. Nonetheless, these models are a bridge to quantifying local delivery, which has always been a challenge for nasal suspensions. The predictive nature of these models could be the link to routine use of the Q3 metrics, such as nasal casts described above, for regulatory purposes. Or at minimum, they could identify which parameters of the formulation, device and patient use are most critical for quantifying bioequivalence.

What's next?

This article merely touches on the myriad of possibilities and variables associated with Q3 structural bioequivalence methodology for nasal spray suspensions. Next, additional research is needed to further define the

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most meaningful parameters then validate them in real practice before they are fully applied to a bioequivalence study. The good news is that regulatory bodies are willing to engage in such discussions.

Meanwhile, the information generated still maintains important value to the developer in terms of understanding the impact of manufacturing processes on structural equivalence. It can also lead to deeper insight into formulation stability and product quality. Moreover, Q3 parameters can be used to evaluate sameness and de-risk pharmacokinetic and clinical endpoint studies.

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