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OINDP news
Orally inhaled and nasal drug products

A Q&A with Copley's Clair Brooks on alternative BE approaches in new FDA guidance

A striking feature of recent batches of OINDP product specific guidances (PSGs) is the inclusion of strategies for the demonstration of bioequivalence (BE) that eliminate the need for a clinical endpoint trial. Copley Applications Specialist Clair Brooks discusses evolving test methods within this context, notably realistic aerodynamic particle size distribution (APSD) measurement, focusing on the drive for better in vitro in vivo correlation (IVIVC).

Do the new PSGs eliminate the requirement for a clinical trial?

The short answer is yes. But it is perhaps more accurate to say that the new PSGs provide "alternative" options for the demonstration of BE, one of which avoids the need for a clinical endpoint trial. The "classic" routes remain in place.

Eliminating the need for clinical endpoint trials could help to accelerate generics onto the market while reducing development costs, since such trials are both costly and time-consuming. These are important gains within the context of increasing public access to generic drugs. Indeed, since 2018 the FDA has had the stated goal of creating clear pathways for the demonstration of BE that do not rely on comparative clinical endpoint studies.

At RDD 2024, the FDA gave two presentations on the outlined alternative approaches for the demonstration of BE presented in the new PSGs and highlighted that patient factors make clinical endpoint studies challenging for locally acting OINDPs and, as a result, potentially subject to considerable variability and unpredictability. Under the weight of evidence approach, the enhanced in vitro methods in the new PSGs may provide more accurate, sensitive, and reproducible data. FDA speakers provided guidance as to method development for both realistic APSD and inhaled dissolution, as well as for in-silico studies.

Is this a new approach for the FDA?

Not entirely. The FDA has previously approved abbreviated new drug applications (ANDAs) for OINDPs in the absence of clinical endpoint data, for example, in 2016 with the approval of the first generic mometasone furoate nasal suspension spray. The PSG for beclomethasone dipropionate metered aerosol for inhalation similarly exemplifies the regulators' openness to alternative routes for establishing BE.
However, this latest batch of PSGs mark a major step forward in the breadth of application of the approach and the detail provided. It therefore suggests an evolution in FDA thinking with respect to reducing reliance on clinical endpoint testing.

What products are covered by the new guidance, and what are the potential benefits of avoiding a comparative clinical endpoint BE trial?

The February PSG releases included 14 updates and 6 new guidances for OINDPs. It is these new PSGs that are especially interesting.

While the updated guidances for inhaled products maintain the classic route for the demonstration of BE, the new PSGs include alternative, clearly defined clinical endpoint-free routes for all 5 of the listed inhalation products. The mannitol and zanamivir products are all dry powder inhalers; the other two are suspension metered dose inhalers. With respect to nasal drug products, both revised and new PSGs include alternative approaches for establishing BE. The agency then issued additional similar PSGs for suspension MDIs, DPIs and nasal sprays in May and August.

Active Ingredient	Route	Dosage form	RLD No.
Budesonide / formoterol fumarate / glycopyrrolate	inhalation	aerosol, metered	212122
Formoterol fumarate / glycopyrrolate	inhalation	aerosol, metered	208294
Mannitol	inhalation	powder	022368
Mannitol	inhalation	powder	202049
Zanimivir	inhalation	powder	021036
Naloxone hydrochloride	nasal	spray, metered	208969

Does the guidance call for the adoption of new in vitro testing strategies?

Yes. Although most of the in vitro tests will be familiar – single actuation content (SAC), aerodynamic particle size distribution (APSD), priming and repriming, plume geometry and spray pattern – there are also new and/or extended test requirements. These include realistic APSD, dissolution, and characterization of the polymorphic form of the drug substance, as proposed for zanamivir. Particle morphology of the emitted dose as typically measured by Morphologically Directed Raman Spectroscopy (MDRS) is now increasingly referenced across both classic and alternative strategies for establishing BE.

For completeness, it is also worth noting that the new PSGs additionally call for charcoal block PK studies when demonstrating BE in the absence of a clinical endpoint and highlight the potential benefits of deploying techniques such as computational fluid dynamics (CFD) and physiologically-based pharmacokinetic (PBPK), though application remains optional.

Can you explain the term "realistic APSD" within the context of the standard compendial test setup for APSD measurement?

This is most easily done via a direct comparison of relevant test setups, as shown below. Figure 1A shows a test setup for classic compendial APSD measurements for DPIs; Figure 1B shows a test setup that enables realistic APSD measurements.

Figure 1A – a classic test setup for APSD measurement for DPIs with NGI, standard USP/Ph.Eur. induction port, flow meter, critical flow controller, and vacuum pump

Figure 1B – a comparable test setup for realistic APSD measurement additionally incorporating breathing simulator and mixing inlet, with an Alberta Idealized Throat in place of the standard induction port

The new PSGs recommend using "mouth-throat models of different sizes (e.g. small and large)" to make realistic APSD measurements. In the image of the classic setup (1A), you see a standard, right-angled USP/Ph. Eur. induction port which is known to underpredict deposition in the mouth-throat, a potentially confounding limitation when it comes to demonstrating BE. You see a more clinically representative induction port in the setup for realistic APSD (1B); in this case, the port is the Alberta Idealized Throat.

In addition to using a more representative interface between the device and the impactor, the realistic APSD setup uses a breathing simulator in accordance with the regulatory guidance for realistic APSD measurement to apply "breathing profiles (e.g. weak and strong) that are representative of the entire patient population." In contrast to the compendial methods for orally inhaled products, which specify constant flow rates for APSD measurement in which the applied profile is a sharp-edged square wave, a breathing simulator allows the application of far more clinically representative test conditions via the adjustment of variables such as rate of acceleration to peak flow.

A mixing inlet is also required for the realistic APSD setup in order to decouple flow through the device from flow through the impactor. This is because cascade impactors are constant flow rate devices with calibrated performance at well-defined values (15 to 100 L/min for the NGI, for example). The mixing inlet allows for the use of patient-representative profiles while simultaneously maintaining flow through the impactor at the constant flow rate required for calibrated performance.

Measuring realistic APSD in this way effectively scopes the performance of the test (T) product relative to reference (R) over a broader range of more clinically representative conditions than is afforded by the compendial test setup. In this way, it can help to provide more robust evidence of BE for a specified patient population.

Do you think that the guidance has broader implications with respect to the evolution of in vitro test methods?

It is likely that the new guidance will add impetus to current trends towards the adoption of more clinically representative in vitro test setups. Many are already using setups such as the one shown in Figure 1B to improve IVIVCs, thereby maximizing clinical relevance and the value of in vitro testing in product development. The PSGs add further incentive to adopt such strategies. While simple compendial methods offer the robust and reliable solutions needed for routine testing, notably in QC, realistic APSD setups and other tests that add in vivo insight can minimize and focus in vivo studies, making complementary application a highly productive and cost-efficient strategy.