How the EU and US Are Aligning Guidance for Inhalation Products

The complicated process of taking an inhaled product to market, via development and manufacturing, is prompting the FDA and EMA to join up their thinking to reduce costs and save time

Martin Oliver at Vectura

Generic inhaled products pose additional challenges for developers when compared to an oral dosage form. Not only must the drug itself be proved equivalent to the originator, the developer must also satisfy the regulators that the combination of drug, along with its delivery device, are equivalent.

The timelines are also somewhat different to those for an originator inhaled product – for the originator, the whole development process can take a decade or more, so the final 'to be marketed' device design does not need to be considered at the outset; however, for a generic, the shorter development time means that the choice of final device design cannot be delayed.

In the US, the FDA demands that a company developing any generic product must prove it meets three criteria: pharmaceutical equivalence, bioequivalence, and therapeutic equivalence. A generic is deemed pharmaceutically equivalent if it contains the same active ingredients as the reference product, is administered using the same dosage form and route of administration, has the same strength, and also meets all compendial standards for quality, purity, and identity.

Bioequivalence is achieved if there is no significant difference in the rate or extent of absorption of the active ingredient at the site of action. For an inhaled product, the site of action is a mucosal surface in the lung, and therefore, it is very difficult to measure directly.

To achieve therapeutic equivalence, developers must prove that a generic can be substituted for the reference product, with the same clinical effect and safety profile, under the conditions specified on the label. It is possible to have an equivalent product that is not substitutable, but to be substitutable, a generic must meet all three of these criteria.

Demonstrating equivalence is particularly challenging for inhaled medicines because they are complex product systems, with the product's performance resulting from the interaction of the formulation with both the device and the patient. Additionally, the manufacturing process can have an effect. Comparison with the reference product can be difficult due to batch-to-batch performance variability of the reference products.

The EU takes a slightly different approach, but several factors are common to the two (see **Figure 1**). In both cases, it must be the same drug delivered via the same type of device. However, the concept of substitutability does not exist in the EU; for approval, a generic must meet drug delivery equivalence requirements, whether this is proved using lab tests, pharmacokinetic (PK) or pharmacodynamic (PD) experiments, or clinical trials. In the US, while these criteria also have to be met to gain approval, there is an additional test: does the product have the same operating instructions as the reference? If it does, then it meets the criteria under the US 505(j) ANDA requirements as an AB-rated substitutable product. If it does not, then it is deemed non-substitutable and would follow the US 505(b)2 new drug application (NDA) approval pathway.

The FDA takes a 'weight of evidence' approach to bioequivalence, and will consider the device and the formulation design, which must be backed up by the PK, PD, or comparative clinical studies. While

regulators have interacted with industry for over a decade on the topic, it was not until 2013 that the first product-specific guideline was published for an inhalation product, the salmeterol/fluticasone inhalation powder combination. Now, such guidelines exist for most oral inhaled drug products, with a route to an abbreviated new drug application (ANDA) approval laid down on the basis of weight of evidence.

The guidelines define a range of tests around single actuation content and aerodynamic particle size distribution. In practice, this requires more than 45 different tests across the different life stages, flow rates, and product strengths of a dry powder inhaler (DPI) product creating a large testing programme. Further tests are required for other devices, such as pressurised metered-dose inhalers (pMDIs) and metered inhalation sprays.

Several lessons can be learnt from the FDA approach. First, while the criteria for the formulation are clearly defined around being qualitatively and quantitatively equivalent, referred to by the FDA as Q1/Q2 criteria, some variation is permitted if it can be scientifically justified. However, device similarity is key to the FDA's view of inhaled generics because of the substitutability issue. Obviously, an exact copy of a device is unlikely. In 2017, the FDA published guidance on what information about a device is required to be considered equivalent, including the comparative use studies a device will need to pass. This has been very helpful in allowing sponsors to understand what differences in user interface are permitted.

Subsequent product approvals have provided practical guidance on the level of changes that might be acceptable; a good example is the January 2019 approval of Mylan's Wixela® Inhub® (fluticasone/salmeterol) generic form of GSK's Advair® inhaler. Device development is complex and iterative in nature, whether for a branded product or a generic, but with careful design and evaluation, new devices are likely to be accepted by the regulators.

The FDA has also recognised that the product device may change during the development process. However, its product-specific guidelines reiterate that a sponsor must use the final device design, made via the commercial manufacturing process, when producing pivotal data. This means that the sponsor of an ANDA product will have to commit to large-scale device and product manufacture early in development.

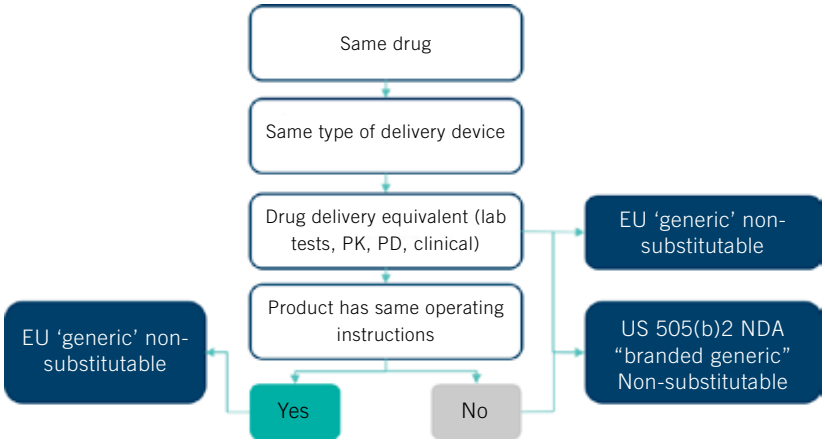

Figure 1: Comparison of the US and EU Inhaled Product Equivalence Pathways

The way patients interact with a device also requires early attention, including proving that it is sufficiently robust. This is now being included in product-specific guidelines from the FDA, which ask for real-world evidence of robustness in patient hands. This is often provided as an add-on to a clinical study design, but with the increasing reliance on alternative *in vitro* tests to replace clinical studies to prove equivalence, other strategies will be required to prove design robustness.

The *in vitro* comparison of a potential generic with the reference product requires extensive testing of multiple product lots, using multiple measures across a number of tests. Data must be produced from at least three batches of both test and reference product, and it is recognised that there can be variability in the performance of the reference product, which can make this process challenging.

A number of alternative approaches are now being considered, which may remove the need for clinical data. The FDA is sponsoring research to develop orthogonal methods that will give a better understanding of the physical process for aerosol drug delivery, deposition in the lung, and absorption. These tests have been collectively named 'Q3 testing'. The requirements are starting to appear in product-specific guidelines as a way to circumvent the need for clinical endpoints, however, the Q3 protocol must be both scientifically justified and validated with the FDA prior to submission.

The FDA's approach to 'weight of evidence' has led to a perception that large clinical studies are required. For inhaled drugs, most of these studies use forced expiratory volume (FEV1) – the amount of air that can be forced from a patient's lungs in one second – as the primary endpoint. This measure comes with a level of variability, driving a

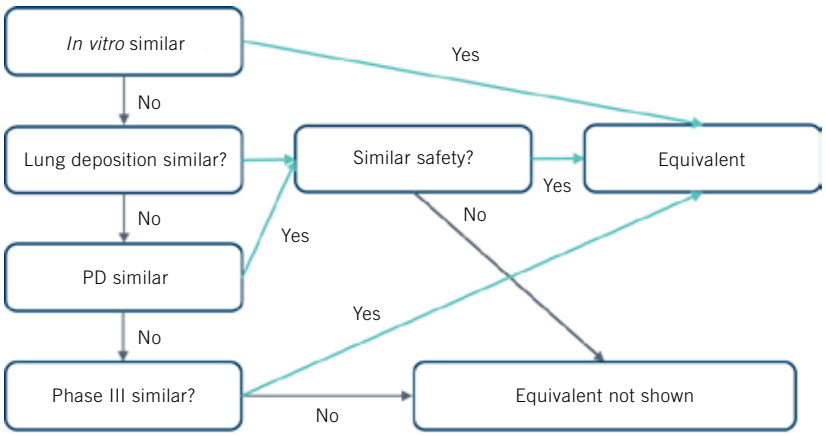

Figure 2: EU Equivalence approach (based on EMA document: ***CPMP/EWP/4151/00 Rev. 1***) (1)

larger sample size to demonstrate equivalence. For example, with corticosteroid drugs, trials lasting two to four weeks may require 1,000 to 3,000 patients, placing a significant burden on the sponsor. Consequently, this level of burden is driving the growing interest in alternative Q3 approaches.

The burden tends to be lower for beta-agonists and antimuscarinic drugs, where single-dose response comparisons in patients are likely to be appropriate. As an example, just 377 patients were required in a trial on tiotropium. This study also had an open-label extension to generate the device and product robustness data that the FDA required. Even if Q3 testing replaces clinical endpoints, there will need to be some real-world evidence showing that the product is robust in patients' hands, which suggests that some evaluation in patients will have to take place.

It is clear that that the FDA is trying to help the industry define a path forward towards showing equivalence in inhaled products. Expectations around the device have been clarified, and there are now some good working examples of guidelines that demonstrate how equivalence can be shown for device designs, accepting that there will necessarily be some level of difference between the generic and the reference product.

In vitro testing for bioequivalence has advanced, including the development of new methodologies that give a broader picture of the physicochemical nature of the aerosolised product, and there is open debate between the pharma industry and the FDA to allow alternative approaches to conducting clinical endpoint bioequivalence studies. However, general quality considerations should not be forgotten in the drive to demonstrate bioequivalence: a generic still has to work consistently, be robust, and therapeutically equivalent in the hands of the patient.

On the other hand, the EU has a stepwise approach to defining bioequivalence, as shown in **Figure 2**. Ultimately, like the FDA, the EMA is looking to show *in vitro* similarity; if that does not exist, it checks lung deposition and PK data. If these results and safety data are similar, then the two products will be deemed equivalent. If not, then PD data are considered, and if that is not similar, a Phase III clinical study will be required.

In reality, most generics are approved by the EMA with an *in vitro* plus PK data package; very few have managed to meet the requirements for *in vitro* similarity using the criteria as they are written. How this trend changes as Q3 testing becomes more widely accepted is, as yet, unknown.

Canada and Brazil have taken a very similar approach to the EU, with added elements in the way that the FDA looks at data. China recently issued guidelines that are broadly similar to the EU approach, but which take in aspects of the US guidelines as well. Globally, the view of inhaled products is starting to align around key pieces of information.

The regulatory environment for inhaled generic medicines is complex, but offers opportunities and pathways for the development of complex inhaled generics. Device design, demonstrating product robustness, and early scale-up are critical to a successful product. The new *in vitro* methods and approaches to product characterisation that are now appearing may reduce the time and cost to demonstrate bioequivalence. This gives developers and innovators the opportunity to characterise products in a way that was previously unattainable, with the aim of reducing both time and cost of drug development.

References

1. *Visit: www.ema.europa.eu/en/documents/scientific-guideline/guideline-requirements-clinical-documentation-orally-inhaled-products-oip-including-requirements_en.pdf*

Martin Oliver is Senior Vice President of Delivery Management – DPI & pMDI Platform at **Vectura**, a specialist inhalation CDMO. Vectura has a Joint Venture in China, the Tianjin Kinnovata Pharmaceutical Co. Ltd, to establish DPI products for the region, where Martin also acts as the Deputy Chairman on the board. He holds a Bachelor of Pharmacy degree from the University of Bradford, UK.