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DEVELOPING AN *IN VITRO* DISSOLUTION AND RELEASE SYSTEM FOR ORALLY INHALED DRUG PRODUCTS

In this article, Robert Price, PhD, Chief Scientific Officer, Nanopharm, critiques regulatory routes for the development of generic OINDPs, runs through recent announcements and developments of note from regulators, and describes how Nanopharm has pioneered the concept of structural Q3 equivalence.

Why do so many switchable generic pulmonary therapies fail at the final hurdle, causing immeasurable frustration and incurring very measurable, non-recoverable costs of several millions of dollars? That's one of the questions we aim to answer in this article.

We will explore an alternative bioequivalence pathway to the current US FDA weight-of-evidence approach – and the need to develop *in vitro* studies that measure the local rate and extent of absorption of a representative lung dose. These scientifically valid measurements are critical in supporting the FDA's concept of microstructural Q3 equivalence testing for locally acting products, essentially increasing the evaluation of pharmaceutical equivalence through physicochemical and functional product characteristics.

Finally, we will present a next-generation, patented, aerosol dose collection apparatus that can harmonise both *in vitro* dissolution and *in vitro* release testing of orally inhaled drug products (OIDPs) – removing the guesswork and providing pharma partners with an unprecedented level of confidence to submit, safe in the knowledge that the data is robust.

THE CURRENT STATE OF PLAY

The current Q1, Q2 weight-of-evidence approach requires a comparative clinical endpoint bioequivalence (BE) study for an abbreviated new drug application (ANDA) of all orally inhaled and nasal drug products (OINDPs). Datamonitor's 2015 *Catalyst Report: A regulatory and economic analysis in Europe and the US*, suggests that the weight-of-evidence approach costs more than US$100 million (£81 million) to bring any AB-rated (i.e. that meet BE standards as demonstrated by *in vivo* and/or *in vitro* testing compared with an approved reference standard) inhaled drug to the US market. The cost of a single, 900+ person clinical endpoint BE study is circa $45 million. These studies typically have high variability and low sensitivity, and cannot detect any formulation differences between test and reference products. They really only confirm local equivalence.

For this reason (and in their words) "even though there is a current, clear regulatory pathway utilising the weight-of-evidence approach for BE assessment of OINDPs",

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the FDA's Office of Generic Drugs (OGD) has recognised the need to find more sensitive and surrogate Q1, Q2 and Q3 based approaches (see Figure 1 for definitions) to demonstrate BE assessment of OINDPs. The need is to find approaches that are more cost and time sensitive. Historically, there have been very limited alternatives to clinical endpoint BE studies for OINDPs. Today, regulators and companies like Nanopharm are actively engaged in the development of both existing and novel *in vitro* techniques to aid the deformulation of the reference listed drug (RLD) and establish Q3 bioequivalence for these complex generic development programmes.

Inhaled biopharmaceutics and the development of new alternate BE approaches using a collective weight-of-evidence from *in vitro* studies will become critical in the development of bioequivalent, locally acting OINDPs.

STOP GAMBLING AND START INVESTING SMARTLY

Sandoz has tried and failed to launch a generic alternative to GlaxoSmithKline's respiratory blockbuster Advair, incurring a $442 million development cost in the process. In October 2016, Sandoz filed a citizen petition with the FDA asking that the agency delay approval of any abbreviated new drug applications (ANDAs) for a generic version of Advair Diskus until pharmacokinetic (PK) BE testing could be shown to account for batch-to-batch variability in the reference drug. In March 2017, the FDA denied the citizen petition on technical grounds.

Although the PK plasma concentration is disconnected from a clinical response, it does appear to be directly related to the physicochemical and release characteristics of the active drug. PK studies suggest that successful *in vitro* based equivalence of the aerodynamic particle size distribution (APSD), as per the product specific guidance, may not directly ensure *in vivo* equivalence in pulmonary absorption, safety profiles and therapeutic efficacy of the test with the RLD.

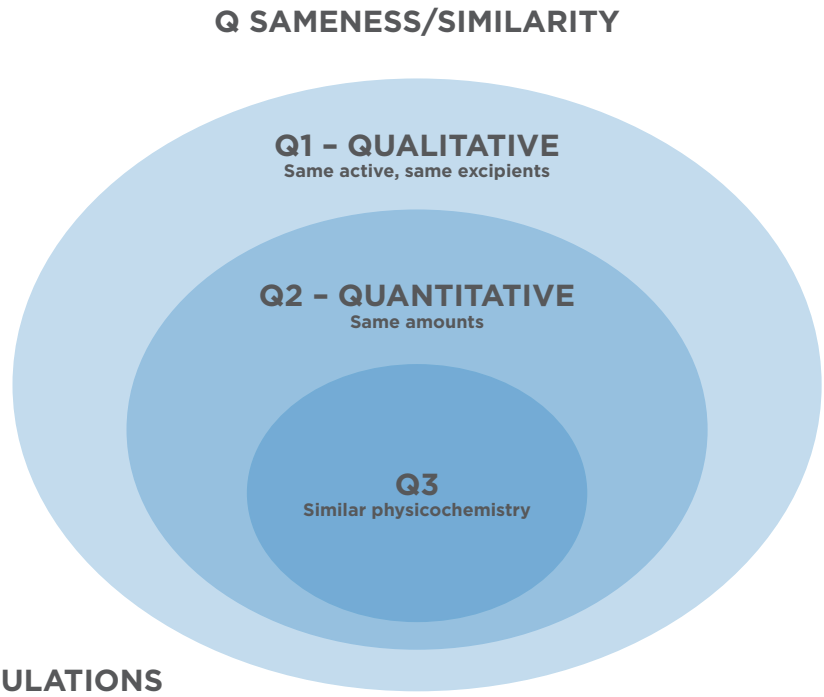

Figure 1: Q1, Q2 and Q3 definitions for sameness and similarity.

The bottom line is that RLD batch selection for BE testing is a lottery. The critical quality attributes are a moving target and, unless we can characterise and understand the source of RLD variability, we will continue to witness expensive failures. We require a combination of advanced *in vitro* aerosol performance testing and access to appropriate and validated physicochemical characterisation methods to enable rapid reformulation of RLD batches, as well as assessing Q3 equivalence as part of an *in vitro* BE weight-of-evidence approach.

THE CONCEPT OF MICROSTRUCTURAL EQUIVALENCE

The 2003 Federal Drug and Cosmetic Act, section 505(j)(8)(A)(ii)[1] states: "For a drug that is not intended to be absorbed into the bloodstream, the Secretary may assess bioavailability by scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of action."

> "*In vitro* dissolution and/or *in vitro* release testing has successfully provided a means of evaluating the release properties through the integrated effects of several physical and chemical properties of a formulated product."

The FDA has now introduced the concept of microstructural (Q3) equivalence to address these measurements for locally acting products. Q3 increases the evaluation of pharmaceutical equivalence to physicochemical and functional product characteristics, and provides a real step change in approach. Q1 only evaluates the same components while Q2 only evaluates the same components in the same concentration. But finding a comparable RLD has been a lottery based on luck rather than science.

Q3 provides for the same components in the same concentration with the same arrangement of matter. ANDAs have been successfully approved based on Q1/Q2 with Q3 approaches for locally acting gastrointestinal (GI) oral products, and transdermal and nasal products. We have also seen recent and significant progress in Q3 evaluations for topical semi-solid dosage forms, led by the FDA. These product-specific guidances provide specific physicochemical characterisation requirements (e.g. rheology, particle sizing, polymorph identification) for comparing the physical and structural similarity for each batch of test and RLD product

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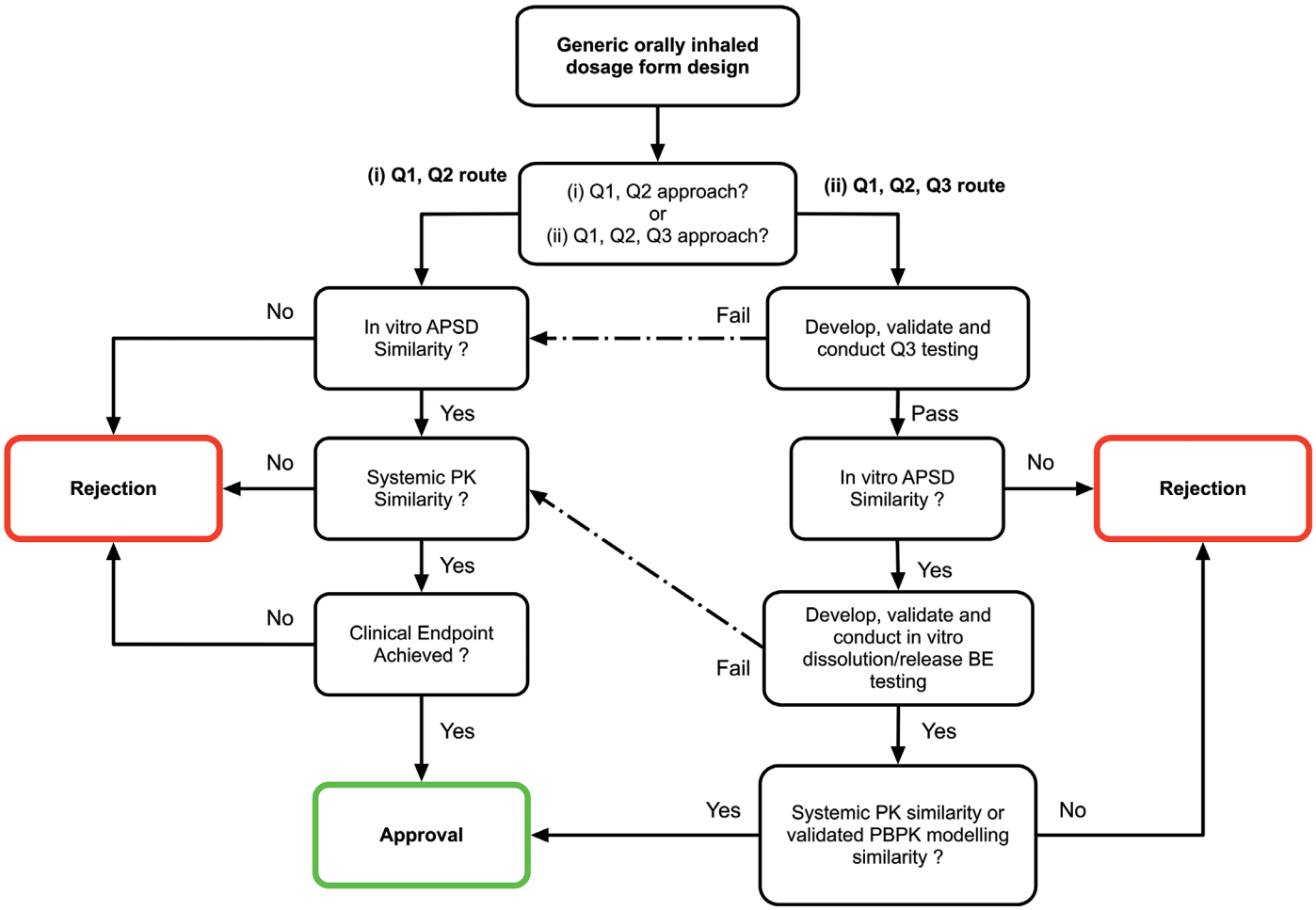

Figure 2: A new approach to bioequivalence.

up and post-approval changes (SUPAC-SS) guidelines: "*In vitro* release testing has shown promise as a means to comprehensively assure consistent delivery of the active component(s)."

In a recent move, the FDA has provided, for the first time, a possible alternative non-clinical BE pathway for an ANDA submission of a solution MDI (Teva's Qvar Redihaler).[2]

Nanopharm has pioneered the concept of structural Q3 equivalence for OINDPs. SmartTrack uses methodologies to bridge *in vitro* measurements and *in vivo* performance of OINDPs through clinically relevant mouth-throat models, dissolution testing, advanced *in silico* modelling and simulation tools (Figure 2). Using its proprietary aerosol collection apparatus, Nanopharm investigates the *in vitro* dissolution, formulation microstructure and realistic aerodynamic particle size distribution performance of generic and reference products with representative mouth-throat models (Figure 3).

These data, with realistic breathing profiles, are employed in an *in silico* regional deposition model with physiologically based pharmacokinetic simulation of both local and systemic exposure. SmartTrack has proved indispensable in guiding product development programmes, and local bioavailability and BE assessment of OINDPs, as well as supporting regulatory decision making.

> "The big hurdle to date in the development of Q3 tools has been that the mode of aerosol collection has lacked uniformity."

IN VITRO RELEASE TESTING

A new addition to the SmartTrack portfolio service offering is *in vitro* release testing (IVRT). With the exception of a range of lipophilic inhaled corticosteroids (ICSs), the aqueous solubility and dose number of the majority of respiratory based products are not dissolution-rate limited in the airway surface liquid (ASL) of the lung (Figure 4). Each aerosolised product will require specific, product-by-product based physical and structural Q3 testing. This is in addition to the development of validated *in vitro* release testing for the demonstration of comparative *in vitro* drug release rates of the active drug from the representative lung dose between test and reference aerosolised products.

While an *in vitro* release test is not expected to directly correlate with, or be predictive of, *in vivo* BE, the measurement of the *in vitro* release rate (IVRR) can provide a comparative test of the local rate of release of the active drug between test and RLD batches. *In vitro* release testing can also be useful as a characterisation tool of finished product performance in controlling both device and formulation variables as well as assessing stability issues over time.

The bespoke IVRT system has been developed specifically to measure the release rate of the impactor stage mass (ISM) of an aerosolised product, using Nanopharm's validated dose-independent Q3 aerosol dose-collection apparatus. In the weight-of-evidence approach, population BE

Figure 3: The smart method for aerosol collection.

> "The current weight-of-evidence approach is a $442 million gamble. RLD batch selection is a lottery based on luck rather than science."

testing of the *in vitro* is undertaken on the ISM, which is defined as the sum of the drug mass on all stages of the impactor, excluding the top impactor stage because of its lack of a specified upper cut off size limit.

The big hurdle to-date in the development of Q3 tools has been that the mode of aerosol collection has lacked uniformity. The critical element is to develop a methodology that can be validated and measures the key quality attributes of drug release – in a uniform way. In response, Nanopharm has developed a proprietary aerosol dose collection system for both Q3 physicochemical characterisation and *in vitro* dissolution and release testing of OIDPs.

The IVRT system has been engineered as an immersion cell system, initially developed as an *in vitro* performance test of drug release from topical semisolid dosage forms.

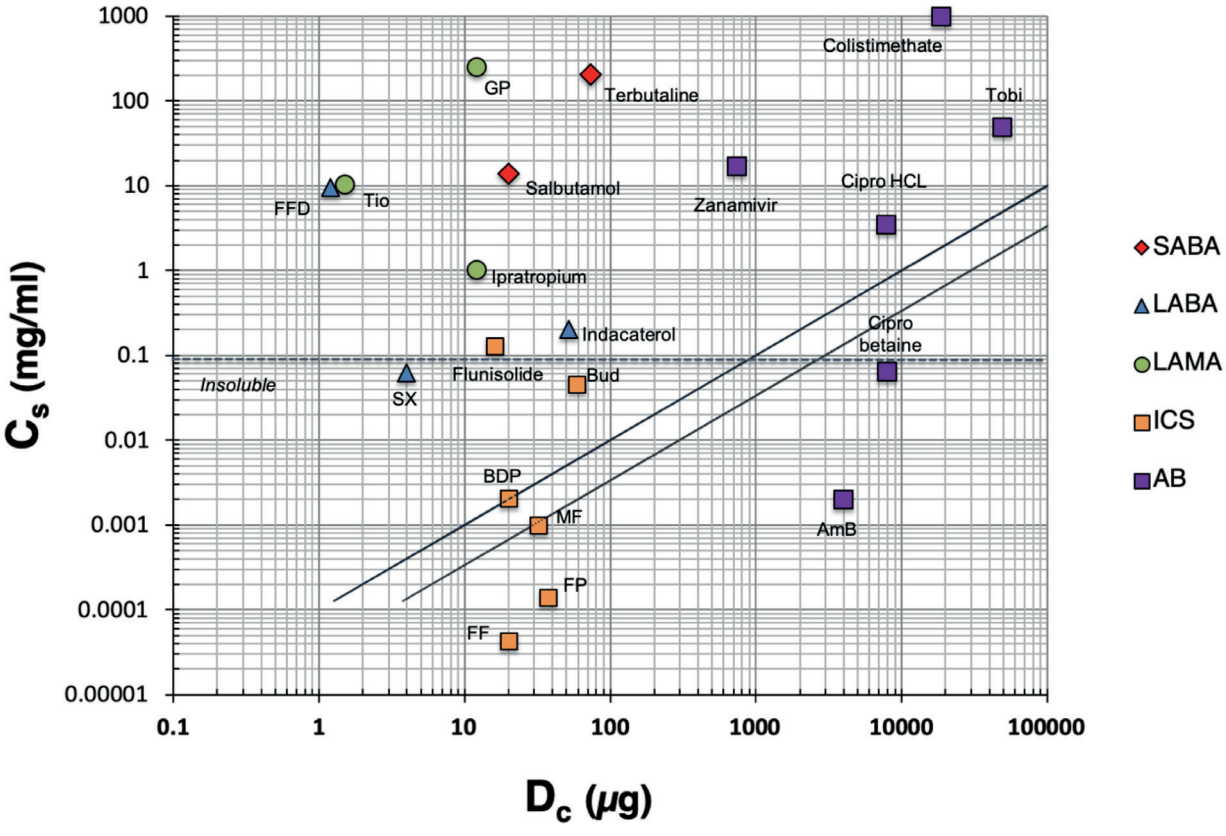

Figure 4: Comparative dissolution rates of various inhaled APIs.[3]

The IVRT system is illustrated in the Higuchi plot of the differences in the *in vitro* release rate of beclomethasone dipropionate from a Fostair 100/6 solution metered dose inhaler (MDI) and a Fostair 100/6 NEXThaler dry powder inhaler (DPI) (Figure 5).

For equivalent ISM doses, the *in vitro* release rate reflects the difference in the physical state of the dispersed active drug. This difference in the physical state between these dispersed aerosolised products can be described by microstructural differences and are characterised by physicochemical properties such as polymorphic form, aerodynamic particle size and shape.

CONCLUSION

It is clear that inhaled biopharmaceutics and the necessary *in vitro* tools required for predicting clinically relevant endpoints of safety and efficacy have become significant in the development of bioequivalent OINDPs.

The current weight-of-evidence approach is a $442 million gamble. RLD batch selection is a lottery based on luck rather than science. We have established, through robust simulations, that the dissolution rate is the key to drug retention in the lung, and that this is the catalyst for more successful developments of reliably bioequivalent formulations and products.

The FDA has introduced, and is championing, the concept of microstructural (Q3) equivalence, with ANDAs approved based on Q1/Q2 with Q3 approaches for locally acting GI oral products, and transdermal and nasal suspensions.

At Nanopharm, we have pioneered the concept of structural Q3 equivalence for OINDPs, providing valid and reproducible approaches for topical generic product equivalence – in turn, reducing the time and cost barrier associated with new generic drug development.

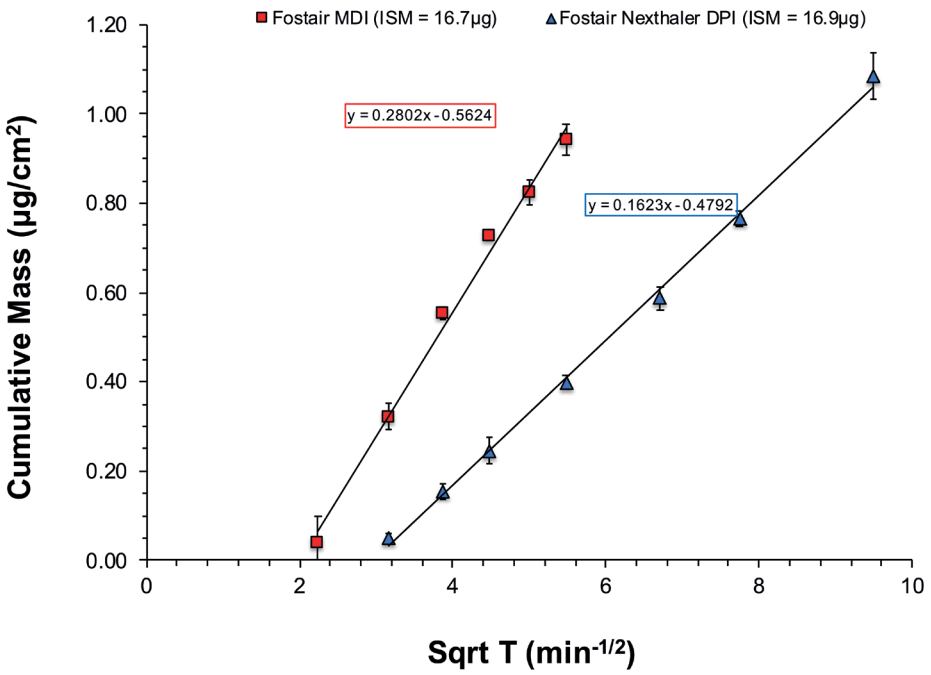

Figure 5: Higuchi plot of the differences in the in vitro release rate of beclomethasone dipropionate from a Fostair 100/6 solution MDI and a Fostair 100/6 NEXThaler DPI.

ABOUT THE COMPANY

Nanopharm, an Aptar Pharma company, is a specialist contract research organisation (CRO) offering product design and development services for orally inhaled and nasal drug products (OINDPs). Nanopharm operates a fee-for-service model, helping its clients navigate the scientific, technical and regulatory challenges in developing nasal and respiratory drug products from discovery through to clinical investigations. It provides an integrated drug development service covering advanced materials characterisation, device and formulation development, and inhaled biopharmaceutics.

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ABOUT THE AUTHOR

Robert Price is the Chief Scientific Officer and Founder of Nanopharm (now an Aptar Pharma company), and Professor of Pharmaceutics at the University of Bath (UK). His research addresses the relationship between the physical, chemical and interfacial properties of materials and their influence on the microstructural properties of complex formulations.

Dr Price graduated with a BSc in Physics and a PhD in Physical Chemistry from University of Wales College of Cardiff. After several years as a post-doctoral research fellow, he joined the Department of Pharmacy and Pharmacology at Bath in 2000, and was awarded a personal chair in 2008. During this time, he also co-founded and successfully grew Nanopharm to become a leading provider of orally inhaled and nasal drug product design and development services. He has authored more than 120 research articles and has been granted a number of patents. He has received the Royal Pharmaceutical Society Science Medal and the Royal Society of Chemistry Innovation Award for his research.