nanopharm SmartTrack™

Your alternative solution to clinical end-point bioequivalence

SmartTrack™ offers the alternative solution to the updated FDA approval process for generic respiratory products.

On 15th May 2019, the FDA provided, for the first time, an alternative pathway to the currently recommended comparative clinical endpoint bioequivalence (BE) study for an abbreviated new drug application (ANDA) submission of a solution metered dose inhaler (Qvar Redihaler), (https://bit.ly/2JOIk96).

Nanopharm are leaders in the provision of scientific based solutions in enabling alternative BE clinical endpoint approaches for orally inhaled generic products. Our SmartTrack process offers a series of services that combine the recording of breath profiles with realistic aerodynamic particle size distribution performance testing, using representative mouth-throat models, in-vitro dissolution and morphology directed particle sizing and chemical imaging of a representative lung dose and regional deposition modelling, together with physiologically-based pharmacokinetic (PBPK) models for predicting local and systemic exposure. SmartTrack offers all the critical elements to meet the alternative BE requirements to clinical endpoint BE studies.

The huge cost of clinical trials

Datamonitor has forecasted that companies would need to spend in excess of $100m in bringing any AB rated inhaled drug to the US market. The estimated cost of a single, 900+ person clinical endpoint BE study would be $45m – some 45% of the total spend. The lengthy and costly clinical endpoint BE study for confirming local equivalence, within the weight-of-evidence approach, has low sensitivity and is unable to detect any formulation differences between test and reference products.

An alternative to clinical endpoint BE would dramatically decrease program costs and increase the net present value (NPV) of respiratory generic products. To date, the total number of FDA product specific guidance (PSG) for orally inhaled and nasal drug products is 26. This would imply the total estimated value of removing clinical endpoint BE studies for both nasal and inhaled products would be in excess of $5 billion.

The new FDA BE guidance for Qvar Redihaler (May 2019)

"…For this particular drug product, which contains a solution-based formulation, if the T formulation is Q1 and Q2 the same as the R formulation, and if the T device is sufficiently similar to the R device with respect to critical design attributes and user interface, additional supportive data may provide a foundation to help ensure the equivalence of T and R products at the local sites of action in the lungs, and thus, could be considered as a potential alternative to the currently recommended comparative clinical endpoint BE study, in the context of the weight-of-evidence approach.

Additional supportive in vitro studies may include, but are not limited to, (i) more predictive APSD testing using representative mouth-throat models and breathing profiles, (ii) characterization of emitted aerosol sprays with respect to velocity profiles and evaporation rates, (iii) dissolution, and (iv) morphology imaging comparisons, including characterization of the full range of residual drug particle sizes. Potential applicants may also consider the use of quantitative methods and modelling (for example, physiologically-based PK and computational fluid dynamic studies) and alternative in vivo PK BE studies".

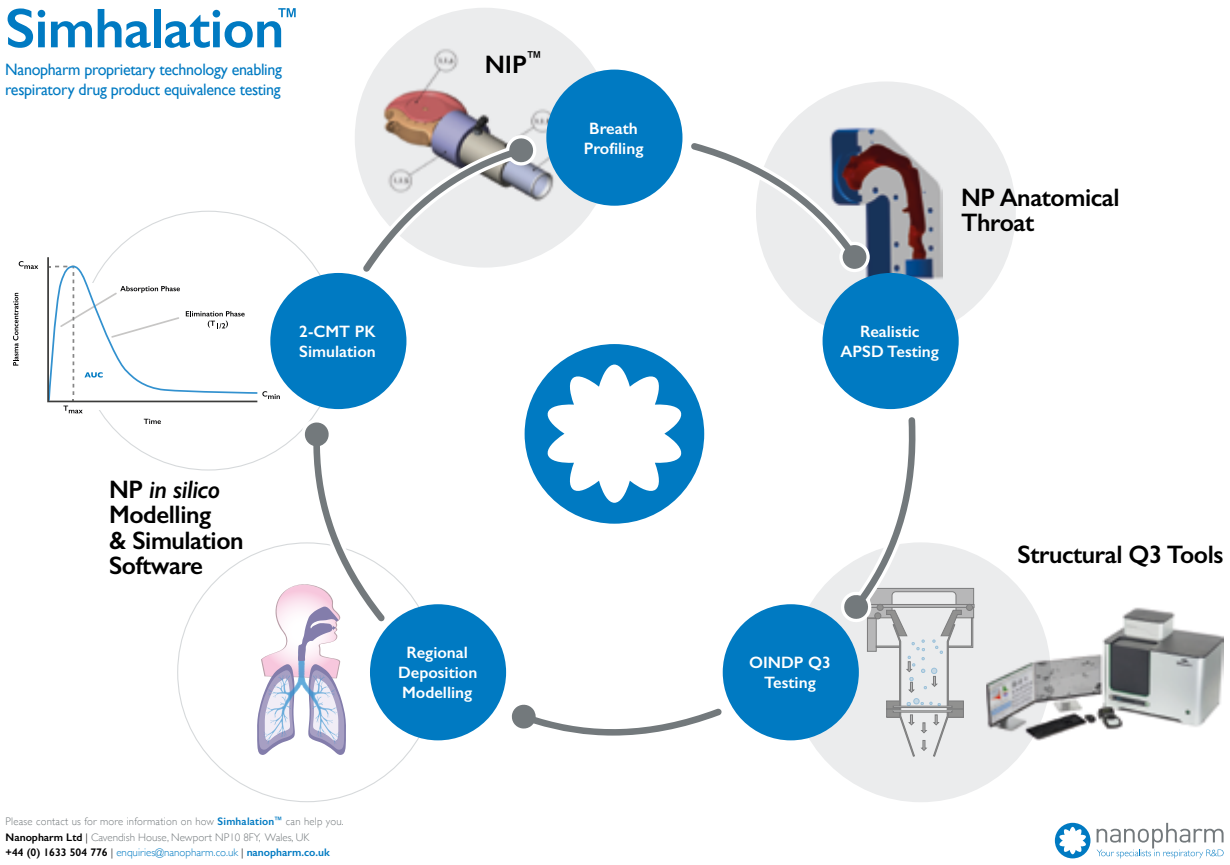
How SmartTrack supports the requirements for an alternative BE approach

SmartTrack has been specifically developed by Nanopharm to expedite the requirements of an alternative BE approach for orally inhaled and nasal drug products. Through the use of our proprietary aerosol collection apparatus (UniDose), Nanopharm can investigate the in-vitro dissolution, formulation microstructure and realistic aerodynamic particle size distribution (APSD) performance of test and reference products with representative mouth-throat models. These data together with realistic breathing profiles are employed in an in-silico Regional Deposition Model (RDM) with physiologically-based pharmacokinetic simulation (PBPK - Simhalation) of local and systemic exposure.

The identification and validation of these novel in vitro techniques has been successfully used to predict the local extent and rate to which the active drug from OINDPs is absorbed and becomes available at the site of therapeutic action. SmartTrack has been utilised and implemented by an increasing number of clients and has proved itself indispensable in guiding product development programs, local bioavailability and BE assessment of OINDPs, as well as supporting regulatory decision making.

Insight into advanced in-silico modelling tools

As part of Nanopharm's SmartTrack solution, we provide in-silico modelling and simulation tools that investigate the relationship between in vitro based measurements and predictive regional deposition, and the local rate and extent of absorption of the therapeutic dose from OINDPs. These advanced modelling tools also provide insight into patient-device interaction and information about both local and systemic bioavailability, which can better characterize both critical device and formulation attributes.



Within a clinical setting, the emitted dose, fine particle mass and aerodynamic particle size distribution from a dry powder inhaler is largely determined by the interaction between the device, formulation and inhalation manoeuvre performed by the patient. Nanopharm's Inhalation Flow Profile device (NIP) enables real-time measurement of patients' inspiratory flow profiles and critical measurements of their initial acceleration at the beginning of inhalation (ACC), peak inspiratory flow (PIF), total inhaled volume (TIV) and airpower (AP). These profiles together with clinically relevant mouth-throat and nasal models have shown good in vivo correlations in predicting regional drug deposition and systemic exposure.

With the state of art real-time feedback, NIP has also been successfully employed in clinical PK studies to train patients and to gather critical inhalation profile data of patients during different arms of a longitudinal, crossover clinical trial for soft-mist, metered dose inhalers and dry powder inhalers.

Nanopharm have pioneered the concept of structural equivalence for OINDPs. We believe this alternative approach to seek generic product approval is vital for the industry. The utility of our in vitro dissolution testing methodology and morphologically directed and surface mapping Raman spectroscopy (MDRS), together with validated in silico mechanistic modelling, is guiding alternative approaches for inter-product comparisons that support clinical endpoint biowaivers for OINPD development programs.

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