GENERIC PMDI PRODUCT DEVELOPMENT FOR THE US: KEY CONSIDERATIONS

In this technical paper, Badre Hammond, Associate Director, Business Development, Next Breath, highlights key considerations and addresses strategies that are believed to reduce risk and ultimately speed up the process for getting a generic pMDI product to the US market. The paper will focus on the key considerations and a stepwise approach that we believe are critical in managing the complexities and unknowns around the development of generic pMDIs.

RATIONALE AND INTRODUCTION

Currently there are no generic asthma/COPD inhalers available in the US. This includes both categories of standard asthma treatment: rescue medication for quick relief and controller medications for long-term prevention. The average cost of these inhaler medicines ranges from US$35-$300 (£21-£180), rendering the treatment expensive for both insured and uninsured consumers.

In April 2013, the US FDA issued a draft guidance for albuterol sulphate.[1] Prior to this, generic companies were reluctant to invest in product development that ultimately may not be acceptable to the FDA. Nonetheless, many pressurised metered dose inhalers (pMDIs) are now approaching patent expiration, and the opportunity is ripe for generics companies wishing to be the first to market and to grab a slice of the US$5 billion pie.

API SELECTION AND EXCIPIENTS

Selecting the proper API and excipients is a key consideration that must be made very early in the ANDA process. Ensuring that the selected API and excipients are comparable to the marketed Reference Listed Drug Product (RLD) is fundamental to achieving *in vitro* bioequivalence (IVBE). A generic formulation must be qualitatively and quantitatively similar to the RLD, which means that the API dose is identical to the label claim of the RLD and the excipient levels in the generic formulation are ±5% of the RLD concentrations. During API/excipients selection, ANDA applicants should source the API from multiple suppliers that have a proven track record of supplying APIs to products in regulated markets. Determination of the correct particle size of the API is critical for suspension pMDIs and will affect IVBE outcomes. The applicant should also request the manufacturer of the drug substance to provide pertinent chemistry, manufacturing, and controls information. Insuring that there is a DMF available (DMF; 21CFR 414.20) for the formulation components is an important step in the selection process.

In addition, a Certificate of Analysis should be requested to substantiate that the batch meets all tests and specifications. Where applicable, the API and excipients must adhere to USP monograph/National Formulary guidelines. Following evaluation of the documentation from the API manufacturer, ANDA applicants should perform a comprehensive screening study of the selected API at their own facility. The goal of this screening study is to confirm that the results generated on-site match the vendor's Certificates of Analysis. This confirmation step may appear trivial or redundant on the surface, but it can and has been a source of many delays, surprises, and wasted resources when the vendor's API specification cannot be reproduced when tested independently.

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Figure 1. pMDI using Landmark® Dose Indicator. (Image courtesy of Aptar Pharma, reproduced with kind permission.)

CONTAINER AND CLOSURE SYSTEM

Unlike most dosage forms that contain formulations in simple packaging systems, pMDIs have unique features; a pMDI, for example that shown in Figure 1, consists of a container, a valve, an actuator (mouthpiece), and the formulation with a highly volatile propellant packaged under pressure. Some pMDIs also incorporate dose counters. The manufacturing process, packaging, and dispensing components play as much of a critical role in the overall success of the product as the formulation itself. These components collectively constitute the drug product that delivers the drug substance in the desired physical form to the biological target.[2] Therefore, all components of the pMDI design warrant a thorough consideration regarding chemistry, manufacturing, and controls and *in vitro* performance. These complex and subtle interactions between the drug substance, excipients, container closure system, and simulated patient use conditions can all have a significant impact on the *in vitro* BE of the Test product to the RLD of the marketed pMDI.

Following a thorough patent examination of the RLD of interest (these are generally available in the FDA's list of Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as The Orange Book), ANDA applicants should engage device vendors early in the development process. This is particularly critical for selecting the metering valve and actuator components given their impact on the aerosolisation and particle size distribution of the drug product. ANDA applicants should ensure that all necessary information for the Container Closure System is provided, including schematic drawings, full descriptions, chemical compositions, regulatory status, and in-house tests and specifications for acceptance or rejection of the aerosol can, actuator, actuator dust cap, and metering valve [21 CFR 211(Subpart E)].[3] This information is typically contained in the Drug Master File (DMF) from the packaging supplier or device supplier and should be referenced appropriately in the regulatory submission.

The FDA CDER's Division of Bioequivalence recommends that the ingredients used in the formulation should be qualitatively identical and quantitatively as close as possible to those of the reference product.[3] In addition, if the RLD pMDI contains a dose counter, the generic equivalent must also have a dose counter.[1] The valve and actuator of the RLD product may be proprietary to the innovator and, as a result, unavailable to ANDA applicants. The Division therefore recommends that the generics companies assure functional equivalence of test and RLD products through both *in vitro* and *in vivo* testing.[2]

In the early engagement process with device vendors, ANDA applicants should request vendors (some of which also supply the innovator) to provide alternative pMDI components that are comparable to the RLD device. They should also request data that supports the selection of the alternative test components. Device vendors that understand this paradigm have begun to generate preliminary data using their proposed generic alternatives to the RLD and may be able to provide them to ANDA applicants upon request.

IN VITRO BE TESTING REQUIREMENTS

ANDA applications are required to demonstrate that the proposed generic product is pharmaceutically equivalent [21 CFR 320.1 (c)] as well as bioequivalent [21 CFR 320.1 (e)] to the RLD.[3] One of the key aspects to approval of generic drug products in the US, including locally acting orally inhaled drug

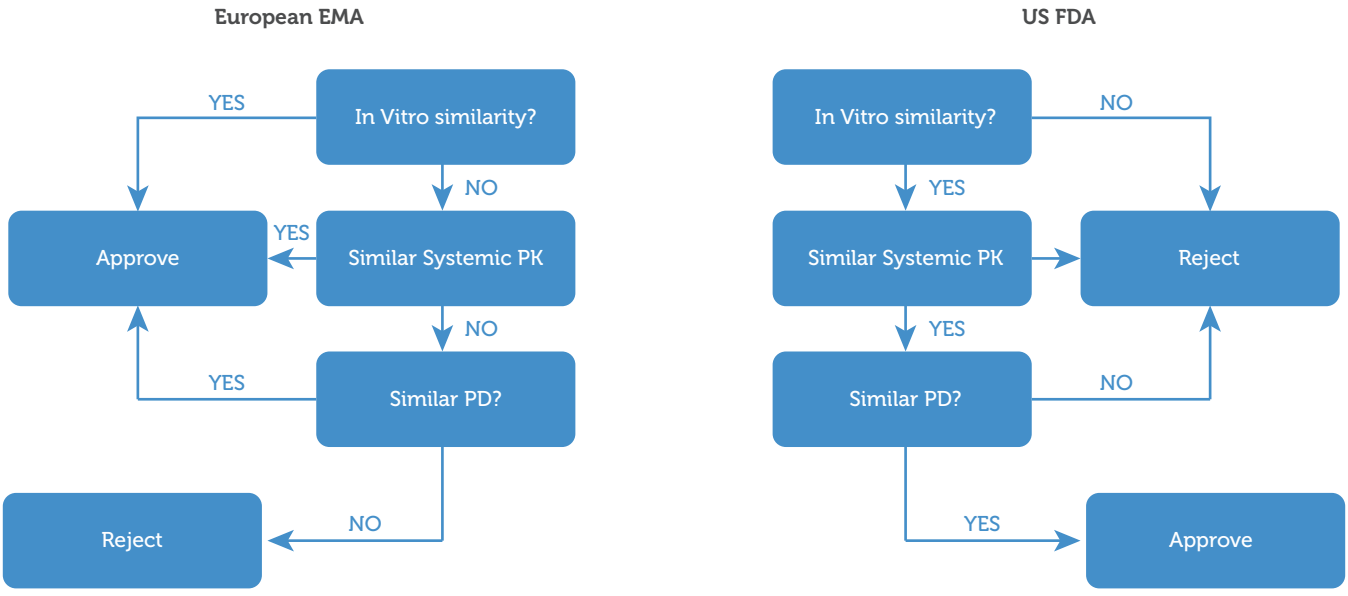

Figure 2: Flow charts comparing EMA and FDA decision processes for assessing IVBE of OIDPs. (Image adapted from Adams et al.[2])

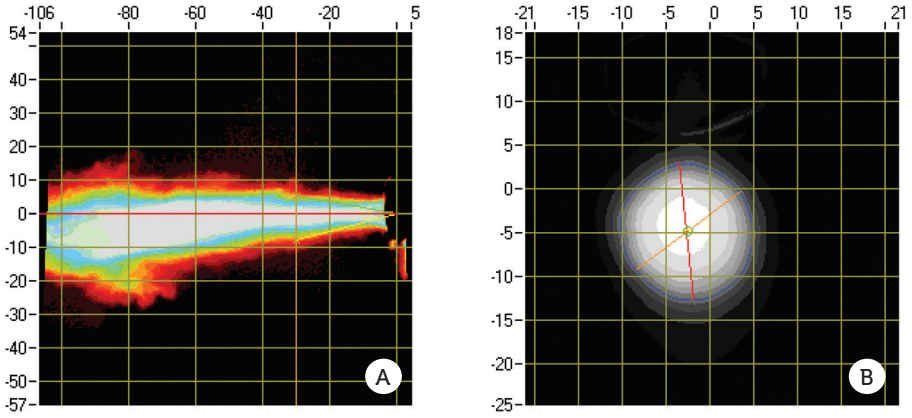

Figure 3: pMDI plume Geometry (A) and Spray Pattern (B) as visualised using Proveris' SprayView® (Image courtesy of Proveris Scientific, reproduced with kind permission.)

products (OIDPs), is the demonstration of *in vitro* and *in vivo* BE. The current US FDA approach for establishing BE of OIDPs is based on an aggregate weight of evidence.[5] It utilises *in vitro* studies to demonstrate equivalent *in vitro* product performance, PK studies to establish equivalent systemic drug exposure, and PD studies or clinical endpoint studies to support equivalence in local drug delivery.[3] It is important for ANDA applicants to ensure that the submission is aligned with the expectations of international regulatory agencies outside of the US. Different regulatory agencies have different recommendations for achieving BE. Figure 2 illustrates the different approaches between the European Medicines Agency (EMA) and the FDA to an ANDA application for OIDPs.[3]

The FDA approves pMDIs as specific combinations of formulation and device. Each of the major components, including specific formulation (propellant and concentrate), and container and closure system (valve, actuator, and container) contributes to the biopharmaceutical performance of the product. In the 2013 draft albuterol guidance, the key metrics for *in vitro* comparison are single actuation content uniformity (SAC), aerodynamic particle size distribution (APSD) by impaction methods, spray pattern, plume geometry and prime/reprime. Images of spray pattern and plume of geometry of a typical pMDI are presented in Figure 3.

One could infer that the types are applicable to all pMDI platforms such as inhaled corticosteroids. Additional studies to quantify the size of API in suspension by microscope or Raman imaging may also be a consideration for suspension-based drug products. The statistical requirements are defined in this guidance and the procedure for calculation of population bioequivalence is defined in a 2012 draft guidance on budesonide.[6,7]

These *in vitro* performance attributes estimate the total and regional deposition of drug substance in the lung and demonstrate quality attributes between test product and RLD, and are therefore central to demonstrating IVBE. In addition, ANDA applicants are required to perform long-term stability (test products only) and comprehensive *in vitro* testing as presented in the CMC guidance for pMDIs and DPIs.[8] For example, applicants should provide data on test products for profiling of actuations near cannister exhaustion for MDIs, the effect of resting time, the effect of storage on the distribution (in case of suspension MDIs), cleaning instructions, and others. (A complete list is available in the CMC guidance).

CONCLUSION

The development and commercialisation of inhaled pressurised products presents a number of unique challenges for ANDA applicants. The complexities in the formulation, device design, performance, and absence of FDA guidance for pMDIs have created a high barrier to entry for new generic inhalers. In addition, innovator companies are making it increasingly difficult for generics by introducing modifications to devices and/or formulations to extend the lives of patents and to secure market exclusivity. For example, Teva introduced a dose counter to its already approved ProAir® (albuterol sulphate) following the FDA Draft Guidance requiring all new pMDIs to include a dose counter/indicator As a result of the guidance, ANDA applicants must now include dose counters on their test products to remain compliant with the sameness paradigm with the RLD.

This article attempts to shed some light on the complexities and the very demanding process of a generic pMDI. It is our judgment that if ANDA applicants follow a stepwise approach focusing on the key considerations discussed above and move to the next phase only if a "Go, No Go" decision is achieved at each stage, the development process will become more manageable.

ABOUT NEXT BREATH

Next Breath, a member of AptarGroup, is a cGMP contract services organisation for pharmaceutical, biotech and medical device companies that bring pulmonary, nasal, and ophthalmic drug products to market. Next Breath provides comprehensive solutions to the development processes from proof-of-concept to commercialisation. Next Breath has led successful submissions for pulmonary and nasal drug products and devices in the US and international markets.

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