

FYs 2013-2017 Regulatory Science Report: Locally-Acting Orally Inhaled and Nasal Drug Products

Introduction

Bioequivalence (BE) is a critical piece of supportive data to show that pharmaceutically equivalent generic drugs perform as expected when administered to patients and can be considered therapeutically equivalent to brand-name drugs. For systemically-acting drugs, demonstrating BE is accomplished using a typical pharmacokinetic (PK) approach - demonstrating equivalence in systemic plasma concentrations of the test product to its reference product. Demonstration of BE for locally-acting orally inhaled and nasal drug products (OINDPs) presents a unique challenge, since the traditional PK approach used for systemically acting drugs is not directly applicable to OINDPs, which deliver drug(s) to the site(s) of action in the lung and nose, respectively.

In the past, performance of OINDPs was difficult to characterize because of a lack of understanding of the complex interactions between active and inactive ingredients, device design and characteristics, and stability across the life of the product. There were no clear in vitro to in vivo correlations and predictive methodologies to determine regional deposition and local availability of these products. To design OINDPs that meet BE standards, the generic industry needed tools that could direct product development toward bioequivalent products.

Even before the authorization of the Generic Drug User Fee Amendments (GDUFA) in 2012, the Office of Generic Drugs (OGD) recognized the need for a path for establishing BE and had been involved in research initiatives that explore paths to establish BE for these complex combination products.

Pre-GDUFA research for orally inhaled drug products (OIDP), metered dose inhalers (MDIs) and dry powder inhalers (DPIs) began with attempts to characterize complex combination products to better understand which characteristics would be critical for the development of generic OIDPs. In 2004, FDA began investigating possible clinical models for assessment of BE for inhaled steroid products, and working with external collaborators on FDA-funded research. Identifying a biomarker would be useful for the demonstration of clinical equivalence, which allows for the inference of BE for these locally-acting products. Measurement of systemic blood values is neither at the site of action nor representative of transport to the site of action (the airways). Drug concentrations cannot be easily measured in the airways, and so some biomarker or pharmacodynamic response would be required to demonstrate that drug has been delivered to the site of action. Between 2009 and 2012, OGD led a series of studies for OIDPs that laid additional groundwork for future research.

For nasal products, FDA published *the Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003). This guidance provided recommendations for studies to measure bioavailability under a New Drug Application (NDA), as well as to establish BE under an Abbreviated New Drug Application (ANDA).

Early research projects and FDA guidance for industry helped establish the initial understanding of complex interactions between formulation, manufacturing, and device, and began development of tools necessary for the evaluation of BE. This research set the framework for GDUFA funded research for OINDPs.

Accomplishments (2012-2017)

The implementation of GDUFA allowed for allocation of resources to better characterize and establish potential tools and methods to investigate the BE of a test product to its reference for complex dosage forms. Initial research confirmed that the performance of OINDPs is governed by complex interactions between device, formulation, and patient factors. In vitro characterizations are the most sensitive methods to establish drug product performance. PK assessments provide assurance that the systemic safety of the test product is not significantly different than that of the reference product. Pharmacodynamics or comparative clinical data provide assurance that there is similarity of delivery to the site of action, and therefore therapeutic equivalence. Together, these parameters provide a weight-of-evidence approach to establish BE for these products, given the complex interactions between device, formulation, and patient factors.

During the first five-years of GDUFA, the FDA published 39 product-specific guidances on OINDPs that include a combination of in vivo and in vitro BE studies (See “Outcomes”).

Orally Inhaled Drug Products

One of the first GDUFA-funded contracts (HHSF223201110117A) was a collaborative effort between FDA, the University of Florida, Virginia Commonwealth University, and the University of Bath. The research collaborative, “PK Comparison of Locally-acting Orally Inhaled Drug Products,” investigated whether pharmacokinetic studies are sensitive enough to detect differences in DPI formulations that differed in central-to-peripheral lung deposition ratios.

Similar to the evaluation for DPIs, FDA funded research to evaluate formulation effects on MDI products. Grant 1U01FD004943 sought to gain understanding of the extent to which MDI product performance depends upon variables, such as amounts and nature of excipients, and drug particle size distributions used. This body of research led to collaborative projects within FDA where FDA focused on methods to streamline the amount of quality data that could be submitted as part of an ANDA to support the in vitro characterization of MDI products. One such project, “Suitability Evaluation of Abbreviated Impactor Measurement (AIM) Method for Characterization of OINDPs” is OGD-led in collaboration with many offices within the FDA’s Center for Drug Evaluation and Research (the Office of Translational Sciences, the Office of Lifecycle Drug Products within the Office of Pharmaceutical Quality, and the Office of New Drugs). The objective of this internal research project is to evaluate the suitability of an AIM method for characterization of oral inhalation products (MDIs and DPIs) as a quality control test, and potentially as an in vitro BE test for generic OINDPs. This internal research project is ongoing.

For MDIs and DPI, how drug particles are deposited in the lung and dissolved in lung mucosal fluid to generate their local action is equally complex. This process is influenced by the interaction of the solid particles with the lung lining fluid and the rate of diffusion of the dissolved drug away from the particle surface. There is no standardized, validated method to measure drug dissolution. Additionally, there is no clear understanding of how in vitro parameters might correlate with in vivo dissolution for these products, i.e., lack of an in vitro to in vivo correlation. For poorly soluble drugs such as inhaled corticosteroids, the rate of dissolution in the airway surface fluid drives the rate of pulmonary drug absorption. Understanding the dissolution process could provide a greater understanding of these complex interactions and eventually predict therapeutic behavior based on these in vitro characteristics. For these reasons, the FDA has been involved in research to create and validate a sensitive and predictive dissolution test system. FDA awarded grants to three sites, each working in parallel on predictive dissolution methods for OINDPs.

Locally Acting Nasal Products

One of the first contracts to be awarded for nasal products was entitled, “To Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical Properties of the Active in Suspension

Nasal Products for Local Action.” This contract began in 2013, and is scheduled to complete in 2018. FDA awarded the contract to the University of Florida, with the University of Bath and Virginia Commonwealth University as major sub-contractors. This contract assesses whether pharmacokinetic studies in combination with in vitro and in silico studies can provide information on the differences in the nasal absorption rate of the drug particles with different particle size within suspension nasal sprays.

Research and Collaboration

Development of Clinically Relevant in Vitro Performance Test for Generic ODPs

Site PI: Michael Hindle (Virginia Commonwealth University)

Grant #: 1U01FD005231-01

09/10/2014- 09/30/2018

PK Comparison of Locally Acting Orally Inhaled Drug Products

Study co-PI: Guenther Hochhaus (University of Florida)

Study co-PI: Robert Price, Jag Shur (University of Bath)

Contract #: HHSF223201110117A

09/16/2011-09/30/2016

Pharmacokinetic Comparison of Locally Acting Orally Inhaled Drug Products

Study PI: Juergen Bulitta (University of Florida)

Contract #: HHSF223201610099C

09/22/2016-09/22/2017

Pharmacokinetic Research Study on the Effects of Different Protective Packaging on the Stability of Fluticasone Propionate Capsules for Inhalation

Study PI: Guenther Hochhaus (University of Florida)

Contract #: HHSF223201300479A

09/30/2013-12/31/2016

Comprehensive Evaluation of Formulation Effects on Metered Dose Inhaler Performance

Site PI: Guenther Hochhaus (University of Florida)

Grant #: 1U01FD004943-01, 5U01FD004943-05

09/15/2013-08/31/2015; 9/01/2015-8/31/2017

An Optimized Dissolution Test System for Orally Inhaled Drugs: Development and Validation

Site PI: Guenther Hochhaus (University of Florida)

Grant #: 1U01FD004950-01

09/15/2013- 08/31/2016

In Vitro Fluid Capacity-limited Dissolution Testing and Its Kinetic Relation to in Vivo Clinical pharmacokinetics for orally inhaled drug products

Site PI: Masahiro Sakagami (Virginia Commonwealth University)

Grant #: 1U01FD004941-01

09/15/2013-02/28/2018

Development of in Vivo Predictive Dissolution Technique to Understand the Clinical Based

Site PI: Robert Price (University of Bath)

Grant #: 1U01FD004953-01

09/15/2013- 10/31/2016

Study to Investigate the Sensitivity of Pharmacokinetics in Detecting Differences in Physicochemical properties of the active in suspension nasal products for local action

Study PI: Guenther Hochhaus (University of Florida)

Contract #: HHSF223201310220C

09/30/2013- 09/30/2018

A Predictive Multiscale Computational Tool for Simulation of Lung Absorption and Pharmacokinetics and Optimization of Pulmonary Drug Delivery

Site PI: Peng Gou (CFD Research Corporation)

Grant #: 1U01FD005214-01

09/10/2014- 08/31/2017

Predictive Lung Deposition Models for Safety and Efficacy of Orally Inhaled Drugs

Site PI: P. Worth Longest (Virginia Commonwealth University)

Grant #: 1U01FD004570

09/14/2012- 09/14/2016

A cluster-based assessment of drug delivery in asthmatic small airways

Site PI: Ching-Long Lin (University of Iowa)

Grant #: 1U01FD005837

09/10/2016- 08/31/2018

Development of Hybrid CFD-PBPK Models for Absorption of Intranasal Corticosteroids

Site PI: Jeff Schroeter

Grant #: 1U01FD005201-01

09/14/2014-08/31/2017

Key Outcomes

Orally Inhaled Drug Products

The research projects for OIDs have led to 31 poster and podium presentations at national and international scientific meetings, and 41 publications. The work provided insight into many processes and critical parameters involved in the understanding of these complex, orally inhaled dry powder and metered dose inhaler products, including: how differences in formulation may affect physicochemical characteristics of OIDs, how new methods and tools can be created and utilized for evaluations of bioequivalence, and how dissolution methods can be utilized to develop a better understanding of the in vitro to in vivo correlation of these locally-acting products.

FDA has gained a better understanding of many elements of BE for OIDs: how chemistry, manufacturing and controls processes can influence bioequivalence; that modifications in device can affect product performance; that complex interactions of surface properties of carrier excipients in dry powder formulations can alter drug delivery; and how variations in excipients may impact particle size and drug product characteristics in these inhaled drug products.

This research allowed FDA to clearly establish the weight-of-evidence approach for regulatory approval of generic OIDs, and to articulate the justifications as to why each piece of the weight-of-evidence approach is critical in the process of determining BE. As a result, FDA published the first product-specific guidance (PSG) for a metered dose inhaler in April 2013 (Albuterol), and the first dry powder inhaler PSG in September 2013 (fluticasone propionate and salmeterol xinafoate). Since then, FDA developed and

published 17 PSGs for these complex products, and provided a roadmap toward ANDA approval in a multi-billion-dollar marketplace lacking generic competition.

FDA looks to use this body of work to streamline the review process by creating tools and methods to simplify the product data for ANDA review, or to better characterize product performance to meaningfully reflect lung deposition, and clinical effects, by establishing an in vitro to in vivo correlation.

Locally Acting Nasal Products

In April 2017, FDA published a PSG for naloxone nasal spray, which is used acutely to treat opioid overdose. The research conducted as part of the GDUFA Regulatory Science program contributed significantly to the characterization and approach to establish BE described in the PSG, which includes both an in vitro and an in vivo method option. This PSG provides potential generic product developers two different methods to establish BE for this critical opioid antagonist. Providing developers with tools to bring new generic products to market may help to bring down costs and allow for greater access to this life-saving drug.

Future Directions

Orally Inhaled Drug Products

In the next five years of GDUFA, there are a few overarching goals for OIDPs. The first goal will be to build on the research of the first five years of GDUFA to create clear pathways to establish BE, without the need for comparative clinical endpoint studies. For example, assessing the sensitivity of the conventional in vitro BE tests to detecting potential in vivo product performance differences between qualitatively and quantitatively (Q1/Q2) the same test and reference inhalation solution products. As well as explore the possibility of in vitro only BE, or BE based on PK and in vitro BE, once a correlation can be clearly identified for lung dissolution. Another project will be to classify suspension inhalation aerosol products based on the complexity of the formulation, and then explore the possibility of an in vitro only BE option for products with a few excipients.

Research looking at computational fluid dynamic (CFD) modelling tools is being developed under a new grant, which began in late 2016 and extends into 2018. FDA awarded grant # 1U01FD005837 to the University of Iowa, for "A Cluster-based Assessment of Drug Delivery in Asthmatic Small Airways. The focus of this work is to incorporate the effects of inter-subject variability on small airways deposition of MDI drug delivery, based on data collected from computerized tomography (CT) scans of asthmatic patients (n=248). The research will provide a set of CFD data that demonstrate the impact of inter-subject variability on small airways deposition of drugs, captured via a cluster-based analysis of the CT data. The study will also incorporate generation of data using gamma scintigraphy, to provide a basis for the validation of these CFD simulations.

A second key development area will be to gain a better understanding of in vitro assessments and their impact on BE, such as the use of dissolution and in silico CFD modelling to predict product performance. The goal will be to provide a robust model for in vitro BE, which can be standardized and utilized for general applicability across the class of products. This could include predictive in vitro testing, such as realistic mouth-throat models, and dissolution testing, and/or predictive in silico models, such as an in vitro only BE method utilizing CFD. Many of the current research models created are candidates, and the goal would be to publish the methodology and key parameters, by publishing new PSGs for products that do not have one currently, and updating currently available PSGs.

Areas of focus for DPI products include exploring advanced tools to develop a deeper understanding about formulation-device interactions, as they influence possible batch-to-batch variability. Research

could develop in vitro tools that can predict in vivo performance, to assess the magnitude and sources of inter-batch variability in DPIs, including possible variations in microstructure leading to variability. Another research aim will be to determine the effect of excipients on dissolution and bioavailability for these products; for example, even if two DPI products are Q1/Q2 with regard to lactose, the topography and charge of the lactose carrier particles, and the amount of fine lactose that could be respirable may be different, and might lead to differences in therapeutic performance.

Another area for exploration is that of new products, including novel formulations and new device considerations. For example, researchers have only a basic understanding of DPI products that utilize a carrier excipient other than lactose, so expanding tools to develop an understanding of these products will be important. Combining with the research models built under GDUFA, FDA can evaluate CFD and other advanced analytical tools to evaluate critical characteristics of devices newer to market, such as those for which spray velocity and spray duration may be the rate-limiting determinants in drug delivery to the site of action in the lung. FDA will also focus on new approaches to more complex products, including two-bronchodilator products, and triple combination inhalation products.

FDA developed the landscape of future research products under GDUFA based on a deep understanding of many new characterization methods and tools developed under the last five years of GDUFA research and innovations from industry and the research community. FDA took into consideration the users of these products. By having a better understanding of these key elements critical to generic drug development and the demonstration of bioequivalence, FDA can create more sensitive, more efficient and less costly methods to evaluate these products, which ultimately can provide the American public with more choices of safe, effective, bioequivalent, and less expensive generic orally inhaled drug products.

Locally Acting Nasal Products

The next five years of research will provide alternatives to comparative clinical endpoint BE studies, and support a better understanding of in vitro, dissolution and modelling tools to be used for ANDA reviews for nasal aerosol and spray products. FDA will apply these tools to new formulations and complex nasal products in development, hopefully to replace the comparative clinical endpoint BE study requirement for ANDAs. FDA will continue work on the development and validation of Morphologically Directed Raman Spectroscopy (MDRS), and other orthogonal methods, such as dissolution and rheological tests for the in vitro only BE assessment of nasal suspension products. Likewise, plan to evaluate some limitations of the MDRS method and explore assessing the user interface of these combination products to better understand what small differences may not produce a clinically meaningful effect for patients in terms of local nasal administration of these products.

Outcomes

Product-Specific Guidances

- Draft product-specific guidance on Acridinium Bromide Powder, metered (Sep 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM460918.pdf>
- Draft product-specific guidance on Albuterol Sulfate Aerosol, Metered (Apr 2013; revised Jun 2013; Dec 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf>
- Draft product-specific guidance on Albuterol Sulfate Aerosol, metered (Apr 2013; revised Jun 2013; Dec 2016)

- <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM346985.pdf>
- Draft product-specific guidance on Azelastine Hydrochloride Spray, metered (May 2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM544813.pdf>
 - Draft product-specific guidance on Azelastine Hydrochloride and Fluticasone Propionate Spray, metered (Jun 2015; revised Jun 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452689.pdf>
 - Draft product-specific guidance on Azelastine Hydrochloride and Fluticasone propionate Spray, metered (Jun 2015; revised Jun 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452689.pdf>
 - Draft product-specific guidance on Beclomethasone Dipropionate Aerosol, metered (Jan 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481768.pdf>
 - Draft product-specific guidance on Budesonide; Formoterol fumarate dehydrate Aerosol, metered (Jun 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452690.pdf>
 - Draft product-specific guidance on Budesonide Powder (Dec 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM533023.pdf>
 - Draft product-specific guidance on Ciclesonide Aerosol, metered (Jan 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481787.pdf>
 - Draft product-specific guidance on Cyanocobalamin Spray (Jul 2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM566389.pdf>
 - Draft product-specific guidance on Fentanyl Citrate Spray, Metered (Apr 2014)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM384118.pdf>
 - Draft product-specific guidance on Fluticasone Furoate Powder (Apr 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495024.pdf>
 - Draft product-specific guidance on Fluticasone Furoate; Vilanterol Trifenatate Powder (Apr 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495023.pdf>
 - Draft product-specific guidance on Fluticasone Propionate Spray, metered (Sep 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461051.pdf>
 - Draft product-specific guidance on Fluticasone Propionate; Salmeterol Xinafoate Powder (Sep 2013)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM367643.pdf>
 - Draft product-specific guidance on Fluticasone Propionate Spray, metered (Sep 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461058.pdf>
 - Draft product-specific guidance on Formoterol fumarate; Mometasone furoate Aerosol, metered (Jan 2016)

- <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481824.pdf>
- Draft product-specific guidance on Formoterol Fumarate Powder (Sep 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461064.pdf>
- Draft product-specific guidance on Glycopyrrolate Powder (Jul 2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM566418.pdf>
- Draft product-specific guidance on Indacaterol Maleate Powder (Apr 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495054.pdf>
- Draft product-specific guidance on Ipratropium Bromide Aerosol, metered (Mar 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM436831.pdf>
- Draft product-specific guidance on Ketorolac Tromethamine Spray, Metered (Apr 2013)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347003.pdf>
- Draft product-specific guidance on Levalbuterol Tartrate Aerosol, metered (Jun 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM452780.pdf>
- Draft product-specific guidance on Mometasone Furoate Monohydrate Spray, metered (Sep 2015)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM461141.pdf>
- Draft product-specific guidance on Mometasone Furoate Aerosol, metered (Apr 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM495387.pdf>
- Draft product-specific guidance on Naloxone Hydrochloride Spray (Apr 2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM554404.pdf>
- Draft product-specific guidance on Nicotine Spray, metered (Jun 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM481943.pdf>
- Draft product-specific guidance on Olopatadine Hydrochloride Spray, metered (Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520248.pdf>
- Draft product-specific guidance on Oxymetazoline Hydrochloride; Tetracaine Hydrochloride Spray, metered (May 2017)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM545027.pdf>
- Draft product-specific guidance on Triamcinolone Acetonide Spray, metered (Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520271.pdf>
- Draft product-specific guidance on Umeclidinium Bromide Powder (Oct 2016)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM520285.pdf>
- Draft product-specific guidance on Zolmitriptan Spray (Jul 2014)
<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM406345.pdf>

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