Boehringer Ingelheim

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Boehringer Ingelheim
Pharmaceuticals Inc.

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061, HFA-305
Rockville, Maryland 20852

October 13, 2012

To Whom it May Concern:

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On behalf of Boehringer Ingelheim Pharmaceuticals, Inc., I herewith enclose a Citizen Petition and accompanying addendum of exhibits requesting the Food and Drug Administration ("FDA") to adopt and apply certain requirements in its review of proposed generic and follow-on versions of SPIRIVA® HandiHaler® under Sections 505(j) and 505(b)(2) of the Food and Drug Cosmetic Act. 21 U.S.C. § 355(j) and 21 U.S.C. § 355(b)(2). I respectfully request FDA to direct any correspondence relating to this petition to me at the above address and facsimile number, and to counsel identified below:

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Thank you in advance.

Sincerely,

S. Li

Sabine Luik, M.D.
Senior Vice President, Medicine and Regulatory
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2012-8678

FDA-2012-P-1072

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CITIZEN PETITION CONCERNING PROPOSED GENERIC AND FOLLOW-ON VERSIONS OF SPIRIVA® HANDIHALER®

TABLE OF CONTENTS

I. ACTIONS REQUESTED

Boehringer Ingelheim Pharmaceuticals, Inc. ("BIPI") herewith submits this citizen petition pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act ("FDCA" or the "Act"), 21 U.S.C. § 355, and FDA's regulations and procedures governing the filing of citizen petitions under 21 C.F.R. § 10.30.[1] In this citizen petition, BIPI respectfully requests FDA to adopt and apply specific requirements that ensure the safety and efficacy of any proposed generic or follow-on product that cites SPIRIVA® HandiHaler® (hereinafter "SPIRIVA") or any other BIPI oral inhalation product containing the active ingredient, tiotropium bromide (hereinafter "BIPI Tiotropium Product"), as the Reference Listed Drug ("RLD").[2]

Acceptance and Filing of Applications

Specifically, BIPI requests that FDA not accept an application for filing under Section 505(j) of the FDCA if the proposed product is not a "duplicate" of SPIRIVA or a BIPI Tiotropium Product. For the purposes of this request, BIPI notes that FDA recently indicated that a duplicate product is one that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as the RLD. Conversely, BIPI further requests that the agency only accept an application for filing under Section 505(b)(2) if the proposed follow-on product is not a "duplicate" of SPIRIVA or a BIPI Tiotropium Product. (*See* pages 18 – 20)

Review and Approval of Applications

BIPI further requests that FDA not approve any application filed under Section 505(j) of the FDCA, 21 U.S.C. § 355(j), for a proposed generic version of SPIRIVA or any BIPI Tiotropium Product unless and until the applicant has:

(1) demonstrated bioequivalence by, at a minimum: developing well-defined protocols with established endpoints for comparative clinical studies; developing and validating *in vitro-in vivo* correlations; establishing statistically justified criteria for declaring bioequivalence; and ensuring that the proposed generic product fully satisfies Q1/Q2 sameness requirements. (*See* pages 7 – 13); and

(2) demonstrated that the proposed generic product carries the same labeling and instructions for use as the RLD, and that any deviation in the design of the device or its operating principles or ergonomics does not change the operating mechanics for the

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[1] As of the date of this petition, BIPI is not aware of any application for a proposed generic or follow-on product that falls within the scope of this petition and is pending before FDA under Section 505(j) or 505(b)(2) of the FDCA. BIPI has not received a notice of paragraph IV certification from any applicant seeking approval of a generic or follow-on version of SPIRIVA HandiHaler. For these reasons, BIPI believes that this citizen petition is not subject to the requirements of Section 505(q) of the FDCA. 21 U.S.C. § 355(q) (2006). *See* Food & Drug Admin., *Guidance for Industry: Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act* (2011), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf.

[2] For the purposes of this citizen petition, the term generic drug product refers to a product that is reviewed under Section 505(j) of the FDCA. 21 U.S.C. § 505(j) (2006). The term "follow-on product" refers to a product that is reviewed under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2) (2006).

patient, which would compromise the interchangeability of the generic and RLD products in the patient's hands. (*See* pages 13 – 17)

BIPI further requests that FDA not approve any application filed under Section 505(b) (2) of the FDCA, 21 U.S.C. § 355(b)(2) for a proposed follow-on version of SPIRIVA or any other BIPI Tiotropium Product, unless and until the applicant has:

(1) conducted a robust clinical program, including clinical studies, that fully addresses all safety and efficacy issues which may arise/appear as a result of any changes or differences in a follow-on product (*See* pages 20 – 26); and

(2) conducted clinical studies demonstrating the efficacy and safety of the proposed product for all indications without extrapolation of the conclusions from one indication to another. (*See* pages 26 – 29)

The scientific and legal bases for these requests are set forth below in detail.[3]

II. STATEMENT OF GROUNDS

A. Background

1. Treatment of Airflow Obstruction in Chronic Obstructive Pulmonary Disease with Tiotropium Bromide

(a) The Toll and Burden of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease ("COPD") is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases.[4] COPD currently afflicts more than 25 million Americans with at least 12 million of those with the disease remaining undiagnosed.[5] Deaths among people with COPD are on the rise. COPD is the fourth leading cause of death in the United States, surpassing cerebrovascular diseases.[6] COPD most often

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[3] On December 16, 2009, GlaxoSmithKline submitted a citizen petition requesting FDA to take certain actions with respect to proposed generic versions of inhalation products containing fluticasone propionate and/or salmeterol xinafoate. *See* Letter from Katharine Knobil, GSK, to Div. of Dockets Mgmt., Food & Drug Admin. (Dec. 16, 2009), Docket No. FDA-P-0597-001 (hereinafter "GSK Petition"). As set forth herein, BIPI endorses the actions requested of FDA in that petition as and to the extent they apply to all orally inhaled drug products, including SPIRIVA and any BIPI Tiotropium Product.

[4] Global Initiative for Chronic Obstructive Lung Disease, *Pocket Guide to COPD Diagnosis, Management, and Prevention: A Guide for Health Care Professionals* 3 (2011), *available at* http://www.goldcopd.org/uploads/users/files/GOLD_PocketGuide_2011_Jan18.pdf.

[5] Am. Lung Assoc., *Understanding COPD*, http://www.lungusa.org/lung-disease/copd/about-copd/understanding-copd.html (last visited June 3, 2012).

[6] *See* Am. Lung Assoc., *Trends in COPD (Chronic Bronchitis and Emphysema): Morbidity and Mortality* 3 (2011), *available at* http://www.lungusa.org/finding-cures/our-research/trend-reports/copd-trend-report.pdf; Datamonitor, *Treatment algorithms: COPD, in Epidemiology and Treatment Algorithm Survey* 11–12 (Dec. 2002); DM Mannino et al., *Chronic Obstructive Pulmonary Disease Surveillance—United States, 1971-2000*, 51 MMWR Surveillance

strikes individuals over the age of 40 who have a history of smoking, and more than 50% of COPD deaths involve women. Smoking is the attributed cause of COPD in 80 to 90 percent of diagnoses.[7] Because of the cumulative effects of smoking in susceptible individuals, a greater proportion of elderly patients with COPD are likely to have more severe disease than patients in younger age groups.

COPD encompasses a range of lung diseases, which result from air flow interference and cause difficulty breathing. The principal cause of such obstruction is "an abnormal inflammatory response of the lungs to noxious particles or gases" inhaled over time while smoking.[8] Chronic bronchitis and emphysema are the two most common conditions of COPD. Chronic bronchitis is caused by swelling of the bronchial tubes, resulting in increased mucus production causing cough, wheezing, and chest tightness.[9] Emphysema occurs when airspaces in the lungs distal to the terminal bronchioles are enlarged, usually resulting from destruction of the air sac walls. The deterioration impedes breathing, particularly during exercise. The coexistence of these conditions results in the characterization of COPD, although it is sometimes difficult to discern from which condition a patient's symptoms may derive.

(b) BIPI Tiotropium Products Approved and in Development for the Treatment of COPD

During the past 15 years, BIPI and its affiliates have invested substantial efforts in the development of new products for the treatment of airflow obstruction associated with COPD and other respiratory diseases.[10] One of those products is SPIRIVA. On the basis of substantial clinical studies conducted by BIPI, FDA approved a new drug application ("NDA") for SPIRIVA on January 30, 2004. With that approval, the product was indicated for long-term, once-daily maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Subsequently, on December 17, 2009, following review of a supplement to the original NDA that focused on two additional clinical studies conducted by

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Summary SS-6, 1–8 (2002) (Exh. 1). *See also* Global Initiative for Chronic Obstructive Lung Disease, *GOLD Teaching Slide Set* 16, *available at* http://www.goldcopd.org/Other-resources/other-resources-gold-teaching-slide-set.html.

[7] Am. Lung Assoc., *Understanding COPD*, http://www.lungusa.org/lung-disease/copd/about-copd/understanding-copd.html (last visited June 3, 2012).

[8] Roberto Rodriguez-Roisin, *The Airway Pathophysiology of COPD: Implications for Treatment*, 2 J. COPD 253, 254 (2005) (Exh. 2).

[9] *See* Mannino et al., *supra* note 6.

[10] Boehringer Ingelheim has long been involved in the development of orally inhaled drug products for the treatment of COPD and other respiratory diseases. Such products include ATROVENT® HFA (ipratropium bromide HFA inhalation aerosol), COMBIVENT® (ipratropium bromide/albuterol sulfate inhalation aerosol), COMBIVENT® RESPIMAT® (ipratropium bromide/albuterol sulfate inhalation spray), BEROTEC® (fenoterol hydrobromide inhalation aerosol), BERODUAL® HFA (ipratropium bromide/fenoterol hydrobromide), and BERODUAL RESPIMAT (ipratropium bromide/fenoterol hydrobromide inhalation solution). The delivery systems for these active ingredients include unit dose solutions for nebulizations, nasal sprays, pressurized metered dose inhalers with both chlorofluorocarbon and hydrofluoroalkane propellants, dry powder inhalers, and innovative, propellant-free MDIs. With these discoveries and developments, Boehringer Ingelheim has developed considerable knowledge about tailored aerosol delivery and safe and effective treatment of respiratory diseases, including COPD.

Boehringer Ingelheim, FDA approved an additional indication for SPIRIVA: reduction in exacerbations of COPD.

SPIRIVA consists of the HandiHaler, a dry powder inhaler ("DPI"), and a drug-containing capsule that is specifically designed and approved to be used with the HandiHaler. The capsule contains a dry powder formulation of the active ingredient, tiotropium.[11] Each capsule contains 18 mcg of tiotropium bromide (equivalent to 22.5 mcg of tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier. Tiotropium bromide is a long-acting, anticholinergic agent, with specificity for muscarinic receptors. It works primarily by binding, reversibly, to muscarinic receptors in the airways, thus preventing the bronchoconstriction of acetylcholine, and resulting in bronchodilation. Long-term maintenance treatment has also been shown to reduce COPD exacerbations. The drug has a large volume of distribution, 32 L/kg, binding extensively to tissues and suggesting a multi-compartment model, where the drug is distributed to more than one physiologic compartment.[12]

The HandiHaler was specifically designed for inhalation of the dry powder formulation contained in the SPIRIVA capsule. Under standardized *in vitro* testing, the HandiHaler delivers a mean of 10.4 mcg tiotropium bromide at a flow rate of 39 L/min for 3.1 seconds.[13] For administration of SPIRIVA, a SPIRIVA capsule is placed into the center chamber of the HandiHaler. The capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler. The tiotropium bromide formulation is dispersed in the air stream when the patient inhales through the mouthpiece. The approved labeling for the product states that it is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler. To that end, physicians are directed to instruct patients about the use of the product and detailed patient instructions for use of the product have been approved by FDA and are part of the product labeling. Moreover, given the importance of ensuring proper use of the product, BIPI routinely distributes placebo capsules in patient training kits to physicians.

Another product currently in development is SPIRIVA® RESPIMAT® (hereinafter "RESPIMAT"). That product is currently under review by FDA, but was approved for use in Europe in 2007 (currently approved in multiple countries worldwide) as a maintenance bronchodilator treatment of airflow limitation in patients with COPD. The RESPIMAT inhaler is a unique, propellant-free device that delivers a metered dose of medication by means of energy released from a spring, rather than through propellants.

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[11] FDA has indicated that the dosage form for SPIRIVA is powder. *See* Food & Drug Admin., *Approved Drug Products with Therapeutic Equivalence Evaluations* App. C (32d ed. 2012), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf [hereinafter *Orange Book*].

[12] Food & Drug Admin., *Review of Pharmacology and Toxicology Data for SPIRIVA HANDIHALER®* 36 (2003), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-395.pdf_Spiriva_Pharmr_P1.pdf; Food & Drug Admin., *Medical Review(s) for SPIRIVA HANDIHALER®* (2004), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-395.pdf_Spiriva_Medr_P1.pdf.

[13] *SPIRIVA Label* 5 (Approved Nov. 4, 2011), *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021395s033lbl.pdf.

2. Statutory Provisions Governing Review and Approval of Generic and Follow-On Products

With passage of the Hatch-Waxman Amendments in 1984, Congress adopted two pathways for approval of drug products that do not require applicants to conduct a full complement of clinical and pre-clinical studies.[14] Those provisions are Section 505(j) of the FDCA, which authorizes FDA to approve generic drugs, and Section 505(b)(2) of the Act, which allows FDA to approve follow-on products in part on the basis of information to which applicants do not otherwise have a right of reference. In connection with its consideration of any application seeking approval of a new drug product under these provisions, FDA is bound by the fundamental purpose underlying the FDCA -- to ensure that all drug products marketed in the United States are safe and effective.[15] Indeed, while FDA is authorized to approve generic and follow-on drugs through these abbreviated pathways, the entry of generic and follow-on products into the marketplace is "subsumed by the overriding necessity of ensuring public access to safe commercial drugs."[16]

(a) Provisions Governing Review of Generic Drug Products Under Section 505(j) of the FDCA

Specifically, under Section 505(j) of the FDCA, an applicant may file an abbreviated new drug application ("ANDA") for approval of a generic drug product. In an ANDA, the applicant references FDA's findings of safety and effectiveness for a previously approved drug product ("reference listed drug" or "RLD").[17] To rely on those findings, the applicant must demonstrate (among other things) that its proposed product is the same as the RLD with respect to active ingredient, dosage form, route of administration, strength, labeling, and conditions of use. 21 U.S.C. § 355(j)(2)(A)(i)-(iii), (v). An ANDA applicant must also show that its proposed product is bioequivalent to the RLD. 21 U.S.C. § 355(j)(2)(A)(iv). If the proposed generic product cannot satisfy these requirements, then there would be no way to assure that FDA's findings of safety and efficacy for the RLD are applicable to the generic drug product.[18]

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[14] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[15] That "essential purpose pervades the FDCA." *See Food & Drug Admin. v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000).

[16] *Schering Corp. v. Food & Drug Admin.*, 51 F.3d 390, 396 (3d Cir. 1995). That is the case even where it is the innovator drug manufacturer that identifies inconsistencies with the requirements of the FDCA. In fact, innovator drug manufacturers such as Bl frequently "possess the scientific data to recognize when FDA may stray from the legislatively mandated testing requirements that impact the safety and effectiveness of the generic drug." S*ee also Mova Pharm. Corp. v. Shalala*, 955 F. Supp. 128, 131 (D.D.C. 1997) ("Faithful application of the Hatch-Waxman provisions ensuring the safety and efficacy of follow-on drugs far outweighs the marginal interest in the availability of follow-on drug products.").

[17] FDA has defined "reference listed drug" to mean "the listed drug identified by FDA as the drug product upon which an applicant relied in seeking approval of its abbreviated application." 21 C.F.R. § 314.3 (2011).

[18] The 505(j) process also permits approval of generic products that are slightly different from the RLDs on which the applications rely. Specifically, for a proposed generic drug that differs from the RLD with respect to dosage form, strength, route of administration, or active ingredient, applicants may file a suitability petition requesting FDA permission to submit an ANDA for such a product. 21 U.S.C. § 355(j)(2)(C) (2006). If FDA determines that additional clinical studies must be conducted to demonstrate the safety and effectiveness of such a proposed generic

Strict compliance with the foregoing requirements is critical because, upon approval of an ANDA (except those that are subject to a suitability petition), FDA designates the generic product as "therapeutically equivalent" to the RLD and assigns an "A" rating to that product in its publication, *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book").[19] As FDA declared therein, "products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[20] The "A" rating means that a generic drug is considered fully substitutable for the RLD. Furthermore, by operation of certain state laws and numerous health insurance programs, FDA's designation of an "A" rating often results in substitution of the generic drug without the knowledge or consent of either the prescribing physician or patient.[21]

(b) Provisions Governing Review of Follow-On Products Under Section 505(b)(2) of the FDCA

Section 505(b)(2) of the FDCA also authorizes FDA to approve a new drug application ("NDA") based on safety and effectiveness (and pre-clinical) data that were not developed by the applicant. Specifically, this provision applies to NDAs for "a drug for which the investigations . . . relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted." 21 U.S.C. § 355(b)(2). There are two types of information on which a 505(b)(2) applicant may rely: published literature and FDA's prior finding of safety and effectiveness for an approved RLD.[22] In the latter case, the applicant may rely on such prior finding only if the application is for a modification to the approved RLD.[23] In turn, FDA may only approve a follow-on product under Section 505(b)(2) if there are sufficient data to support the differences between the proposed drug and the RLD, and the proposed drug product satisfies the statutory approval standard of safety and effectiveness.

An application submitted under Section 505(b)(2) shares elements of both an ANDA and a stand-alone 505(b)(1) NDA. As with an ANDA, a 505(b)(2) application may rely in part on FDA's finding that the RLD is safe and effective as evidence in support of the proposed product's own safety and effectiveness. On the other hand, a 505(b)(2) application is, like a

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product, then FDA must deny the suitability petition and forbid the applicant from filing an ANDA. 21 U.S.C. § 355(j)(2)(C)(i) (2006).

[19] *See Orange Book*, *supra* note 11, at iv.

[20] *Id.*

[21] As of January 2010, the following 16 state statutes require mandatory substitution: Fla. Stat. § 465.025 (Florida); Haw. Rev. Stat. § 328-91 (Hawaii); Ky. Rev. Stat. Ann. § 217.822 (Kentucky); ME. Rev. Stat. tit. 32, § 13781 (Maine); Mass. Gen. Laws ch. 112, § 12D (Massachusetts); Minn. Stat. § 151.21 (Minnesota); Nev. Rev. Stat. § 639.2583 (Nevada); N.J. Stat. Ann. § 24:6E-6 (New Jersey); N.Y. Educ. Law § 6816-a (New York); 35 Pa. Cons. Stat. § 960.3 (Pennsylvania); R.I. Gen. Laws §5-19.1-19 (Rhode Island); Tenn. Code. Ann. § 53-10-205(a) (Tennessee); Vt. Stat. Ann. tit. 18, § 4605 (Vermont); Wash. Rev. Code § 69.41.130 (Washington); W. Va. Code § 30-5-12b (West Virginia); Wis. Stat. § 450.13(1) (Wisconsin).

[22] Food & Drug Admin., *Draft Guidance for Industry: Applications Covered by Section 505(b)(2)* (1999) [hereinafter *Draft 505(b)(2) Guidance*], *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf.

[23] *Id.* at 2.

stand-alone 505(b)(1) application, approved under Section 505(c) and must satisfy the same comprehensive statutory requirements for safety and effectiveness information as a stand-alone NDA. While an ANDA is required to duplicate an RLD (with a few very limited exceptions), a 505(b)(2) application may describe a drug with differences from the listed drug it references. These differences may include any change for which clinical studies (other than bioequivalence studies) are needed to ensure safety or effectiveness of the proposed drug product. 21 C.F.R. § 314.54(a). A product approved under Section 505(b)(2) is not therapeutically equivalent to the RLD, and such products are not referenced as such in the Orange Book.[24]

B. Standards Governing Review of Applications Submitted Under Sections 505(j) and 505(b)(2) of the FDCA

1. FDA Must Apply Strict Requirements in its Review of ANDAs Referencing SPIRIVA or any other BIPI Tiotropium Product

Under Section 505(j) of the FDCA, there are at least two statutory requirements that are especially critical to FDA's review of a proposed generic version of SPIRIVA.[25] 21 U.S.C. § 355(j). First, FDA may not approve an ANDA unless and until it can ensure that the proposed generic drug product is bioequivalent to SPIRIVA. 21 U.S.C. § 355(j)(4)(F). Second, FDA may not approve an ANDA unless the labeling for the proposed generic product is the same as the labeling (and instructions for use) approved for SPIRIVA. 21 U.S.C. § 355(j)(4)(G). As described next, given the difficulties in assessing the bioequivalence of orally inhaled products and the critical nature of the patient-device interface, FDA must apply strict standards and requirements under these statutory provisions to ensure the safety and efficacy of any proposed generic version of SPIRIVA.[26]

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[24] Products approved under Section 505(b)(2) cannot be therapeutically equivalent to their RLDs because they do not meet the basic definition of therapeutic equivalence. That is, there is a difference that renders them not pharmaceutically equivalent to the RLD, or they have not been shown to be bioequivalent to the RLD. *See Orange Book, supra* note 11, at vii (defining "therapeutic equivalents").

[25] As a threshold matter, FDA may not accept an ANDA for a proposed product that is not a duplicate of SPIRIVA unless the agency first grants a suitability petition allowing such an ANDA to be filed. To be sure, the FDCA permits an applicant to submit a suitability petition when its product is in a different dosage form from the RLD. A suitability petition cannot be granted, however, for any difference or change from the RLD that would require clinical studies to demonstrate that such change or difference would not affect the safety or efficacy of the product. Given the complexities of evaluating products like orally inhaled drugs, however, FDA could not grant such a petition for a product that was not a duplicate of SPIRIVA, since clinical studies would certainly be necessary to show the safety and effectiveness of such a product. Indeed, FDA recognized as early as 1994 that simple *in vivo* bridging studies would be insufficient to support changes to orally inhaled drug products and that clinical studies would be unavoidable. *See, e.g.*, FDA's 1994 "Points to Consider" document, where the agency recommended long term safety and efficacy studies to support a switch from one device to another (*e.g.*, MDI to DPI); and FDA's response to the King auto-injector petition: "[S]ome auto-injector changes (*e.g.*, a change to the needle hub assembly, different operating principles, different ergonomics) may require further clinical data because potential clinical consequences might be unknown."

[26] Although BIPI focuses in this citizen petition solely on the bioequivalence and same labeling requirements governing proposed generic versions of SPIRIVA, those are certainly not the only issues with which FDA must be concerned. Other issues surrounding SPIRIVA are summarized *infra* in the sections describing challenges faced by BIPI in the development and manufacture of SPIRIVA and RESPIMAT.

(a) The Requirement of Bioequivalence

(i) Statutory and Regulatory Requirements Governing Bioequivalence Determinations

Since the majority of orally administered drug products reach their site of action through systemic circulation, bioequivalence of a proposed generic product to its RDL is typically based on measurements of the drug concentration in either the plasma or blood. That approach, however, is not considered sufficient to establish bioequivalence for orally inhaled drug products used for the treatment of lung diseases such as asthma and COPD. That is because such products are largely, if not entirely, locally acting and do not appear to materially rely on systemic circulation for drug delivery or intended action.

Specifically, under the FDCA, a generic drug is considered bioequivalent to the RLD if "the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of the listed drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses." 21 U.S.C. § 355(j)(8)(B)(i). Where, as with SPIRIVA and generally with inhaled drugs that are very poorly absorbed into the bloodstream, FDA may assess bioavailability through the use of "scientifically valid measurements intended to reflect the rate and extent to which the active ingredient or therapeutic ingredient becomes available at the site of drug action." 21 U.S.C. § 355(j)(8)(A)(ii). In such cases, FDA is authorized to establish such alternative methods if they are expected to detect a significant difference between the drug and the RLD in safety and therapeutic effect. 21 U.S.C. § 355(j)(8)(C).[27]

In its regulations implementing these statutory provisions, FDA directs all ANDA applicants to "conduct bioavailability and bioequivalence testing using the most accurate, sensitive, and reproducible approach available" among certain methodologies set forth in the regulations. 21 C.F.R. § 320.24(a). In descending order of accuracy and sensitivity, the regulations provide that such methods include (1) *in vivo* pharmacokinetic studies, (2) *in vivo* pharmacodynamic effect studies, (3) clinical endpoint studies, and (4) and *in vitro* studies. 21 C.F.R. § 320.24(b). FDA has indicated that it considers "well-controlled clinical trials that establish the safety and effectiveness of the drug product" or "appropriately designed comparative clinical trials" to be "sufficiently accurate" for dosage forms such as inhalation products where the active moiety is delivered locally to the site of action. *Id.*

(ii) An "Aggregate Weight of Evidence" Approach To Establishing Bioequivalence of DPIs

To date, FDA has not issued any formal guidance to industry setting forth specific standards and tests for assessing the bioequivalence of orally inhaled drug products. That is not

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[27] FDA "must make [a] bioequivalence finding under some reasonable and scientifically supported criterion, whether it does so on a case-by-case basis or through more general inferences about a category of drugs or dosage forms." *Schering Corp. v. Sullivan*, 782 F. Supp. 645 (D.D.C. 1992). The agency must "cogently explain" any decision it does reach; it may not simply issue a "conclusory response." *See Alpharma v. Leavitt,* 460 F.3d 1 (D.C. Cir. 2006); *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484 (D.C. Cir. 1995).

to say, however, that FDA has not recognized the difficulty of establishing bioequivalence for such products. Indeed, as FDA declared in its draft CMC Guidance on MDIs and DPIs, the "concept of classical bioequivalence and bioavailability is usually not applicable for oral inhalation aerosols" or for DPIs.[28] And, as FDA acknowledged in its 2007 document, *Critical Path Opportunities for Generic Drugs*, there are a number of "scientific challenges that need to be addressed to develop generic versions of these products."[29] Thus, the agency has consistently signaled that additional science must be developed before generic versions of oral inhalation products may be approved.[30]

In 2009, scientists with the Office of Generic Drugs at FDA focused specifically on the issues surrounding bioequivalence determinations for DPIs. Such assessments of bioequivalence, they declared, are "more challenging" than establishing bioequivalence for other types of products.[31] Furthermore, they recognized that, switching patients from one DPI to another may cause "confusion to the patient" and result in "ineffective disease treatment."[32] To address these challenges, these officials indicated that the "current thinking" for evaluating bioequivalence of DPIs rests on an "aggregate weight of evidence" approach. That approach would rely on: (1) *in vitro* studies to determine comparative *in vitro* performance of test and reference DPIs, (2) pharmacokinetic (or pharmacodynamic) studies to establish equivalence of systemic exposure, and (3) pharmacodynamic (or clinical endpoint) studies to demonstrate equivalence in local action.

At the same time and in addition to these studies, these FDA officials indicated that compliance with Q1/Q2 sameness requirements will be important to ensure that the formulations

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[28]Food & Drug Admin., *Draft Guidance for Industry: Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation* 3–5 (1998) [hereinafter *CMC Guidance*], *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070573.pdf. FDA went on to explain that "the dose administered is typically so small that blood or serum concentrations are generally undetectable by routine analytical methods. Moreover, bioequivalence studies are complicated by the fact that only approximately 10-15% of the dose reaches the biological target. The remainder of the dose, trapped in the mouth or pharynx, is swallowed and absorbed through the gastrointestinal (GI) tract. Thus, even if determination of blood or serum concentrations were possible, additional and more extensive studies would be necessary to distinguish the contributions of the drug absorbed from the pulmonary, buccal and GI routes."

[29] *See* Food & Drug Admin., *Critical Path Opportunities for Generic Drugs* (May 1, 2007), *available at* www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm#inhalation.

[30] For example, in advance of holding an Advisory Committee meeting in 2008 to consider bioequivalence issues surrounding inhalation drug products, FDA indicated that "no validated methods [for measuring potency] with acceptable sensitivity and precision are available." *See* Food & Drug Admin., *Briefing Information: Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology July 22-23* 161 (2008), *available at* www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4370b1-01-FDA.pdf. Thus, FDA's efforts to evaluate bioequivalence for oral inhalation products are less developed than its actions to assess bioequivalence for nasal sprays (where a guidance document has been issued). *See, e.g.*, Food & Drug Admin., *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (2003), *available at* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070111.pdf.

[31] S. L. Lee. et al., *In Vitro Considerations to Support Bioequivalence of Locally Acting Drugs in Dry Powder Inhalers for Lung Diseases*, 2009 AAPS J. 414, 414 (2009) [hereinafter *Regulatory Note*] (Exh. 3).

[32] *Id.* at 419.

of the proposed generic product and RLD are highly similar, if not the same, as one another.[33] In the context of developing standards to govern bioequivalence determinations for other locally acting products, FDA has previously indicated that it expects a generic product to be qualitatively ("Q1") and quantitatively ("Q2") the same as the RLD ("Q1/Q2 sameness").[34] For DPIs, the FDA officials indicated that such a "formulation equivalence recommendation is generally expected to increase the likelihood of establishing bioequivalence." But, they also declared that "this recommendation alone is not sufficient to ensure bioequivalence" because other formulation factors, such as size, shape, surface properties, and morphology of drug and carrier particles, may also influence the safety and efficacy of the drug product.

(iii) The Science Remains Undeveloped and More Is Needed Before Bioequivalence Can be Demonstrated for DPIs

BIPI agrees that an array of *in vitro*, pharmacokinetic, and clinical studies will be necessary to demonstrate bioequivalence of DPIs, along with Q1/Q2 sameness.[35] There is, however, no question that the science in this regard is still nascent, and new approaches and methodologies will be necessary before any proposed DPI containing tiotropium bromide can be determined to be bioequivalent to SPIRIVA. Indeed, since publication of the FDA paper on bioequivalence determinations for DPIs, the proceedings of at least two FDA-industry workshops have been published that consider the issues surrounding bioequivalence determinations for orally inhaled drug products.[36] As Dr. Woodcock declared when opening one of these workshops, "new scientific approaches are necessary" and (among other items) there is a need to identify new biomarkers, achieve a better understanding of pulmonary pharmacodynamics and *in vitro/in vivo* correlations, and develop new clinical trial designs and better statistical approaches to ensure equivalence of safety and efficacy.[37]

These new approaches are necessary because there continue to be outstanding questions surrounding the utility and reliability of the studies underlying the "aggregate weight of evidence" approach to establishing bioequivalence. One of these concerns centers on the lack of an *in vitro/in vivo* correlation for such products. Specifically, it is now generally accepted that for orally inhaled drug products, *in vitro* dose and deposition characteristics have little predictive value for *in vivo* target organ deposition, active site availability and systemic absorption kinetics

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[33] Q1 sameness means that the test product uses the same active and inactive ingredient(s) as the reference product. Q2 sameness means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product. *See* Wallace P. Adams, *The June 1999 Draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays: History, Recommendations and Local Delivery Issues* 9 (2001), *available at* www.fda.gov/ohrms/dockets/ac/01/slides/3764s1_02_adams.ppt (Exh. 4).

[34] *See* Food & Drug Admin., *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, *supra* note 30, at 11 (noting that for both solution and suspension formulations, the recommended approach relies on qualitative (Q1) and quantitative (Q2) sameness of test and reference formulations).

[35] These will be the minimal requirements and there very well may be additional based on the products at issue.

[36] *See, e.g.,* Wallace P. Adams et al., *Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPS): Workshop Summary Report*, 23 J. Aerosol Med. Pulmonary Drug Delivery 1 (2010) (Exh. 5); *See also* Dennis O'Connor et al., *Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products: Workshop Summary Report*, 24 J. Aerosol Med. Pulmonary Drug Delivery 119 (2011) (Exh. 6).

[37] Adams, *supra* note 36, at 3.

and as a result, have little predictive value for assuring clinical efficacy and safety. This is, in part, due to the differences between the cascade impactor that is used for *in vitro* measurements and the actual geometry of human airways – while cascade impactor testing can characterize aerodynamic particle size distribution, it has not been shown to predict actual lung deposition. *In vitro* methods are also not capable of predicting the potential for differences in patient-device interaction, and any impact on clinical effect. The inability to extrapolate from *in vitro* results to clinical effect has been recognized by FDA officials and recorded in the scientific literature.[38] Indeed, one study found that, while two DPI products with the same formulation, airflow resistance and polymer composition had comparable *in vitro* performance, there were significant differences in the pharmacokinetic profiles of the two products.[39]

At the same time, investigators have expressed concern about the ability of current clinical methods to evaluate bioequivalence for orally inhaled, locally acting products given the nature of the dose-response curve for such products. As contemplated by the aggregate weight of evidence approach, it is necessary to conduct pharmacodynamic (or clinical endpoint) studies to demonstrate local equivalence. Yet, the dose-response relationship at the site of activity for receptor mediated effects is generally S-shaped and saturable in nature, and it is only steep around the EC50 (the concentration inducing 50% of the maximum effect).[40] Thus, it is only possible at that part of the dose-response curve for pharmacodynamic bioequivalence studies to differentiate between test and reference products delivering different amounts of drug or having different effects.

Ascertaining dose response as it relates to certain specific outcomes or surrogates is not always achievable. The dose-response may differ for different endpoints and regional distribution of drug in the lung may play a yet undetermined role in drug efficacy (peripheral vs. more central deposition may occur). For inhaled tiotropium, the dose-response relationship is known for lung-function changes, but is not known for other outcomes, like exacerbations of COPD, and is especially difficult to identify for long-term safety outcomes, as only limited numbers of doses have been and can be investigated in adequately powered long-term studies. Bioequivalence studies, however, will evaluate an effective dose of the RLD and if that dose is in the insensitive portion of the dose-response curve as has been demonstrated for SPIRIVA and

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[38] Senior FDA scientists with responsibility for approving innovator and generic respiratory products authored a relevant paper. *See Regulatory Note*, *supra* note 31, at 422 ("Although the aerodynamic particle size distribution is known to impact lung deposition, its relationships with regional lung deposition and clinical efficacy are not fully understood."); S*ee also* J. Mitchell et al., *In Vitro and In Vivo Aspects of Cascade Impactor Tests and Inhaler Performance: A Review*, 8 AAPS PharmSciTech 110, 110 (2007) (Exh. 7) ("[A]ttempts to use [cascade impactor] generated data from quality control testing to compare products for bioequivalence are likely to have only limited success, as links between laboratory-measured APSD, particle deposition in the respiratory tract, and clinical response are not straightforward.").

[39] In particular, systemic exposure to the active drug ingredients was approximately two-fold greater with one device as compared to the other. The authors suggested that these findings may result from differences in the interaction that the patient has with the device, which is not tested by standardized *in vitro* methods. *See* P. T. Daley-Yates et al., *Pharmacokinetic, Pharmacodynamic, Efficacy, and Safety Data from Two Randomized, Double-Blind Studies in Patients with Asthma and an In Vitro Study Comparing Two Dry-Powder Inhalers Delivering a Combination of Salmeterol 50 µg and Fluticasone Propionate 250 µg: Implications for Establishing Bioequivalence of Inhaled Products*, 31 Clinical Therapeutics 370, 382–83 (2009) (Exh. 8).

[40] O'Connor, *supra* note 36, at 121.

other inhaled drugs, then differences in the delivered dose will not allow one to determine if there are differences in effects, particularly where more than one clinical outcome is relevant and has to be considered.[41] This problem would certainly apply to proposed products containing tiotropium bromide in light of its response curve.[42]

Considering these and other concerns, the participants in a March 2009 workshop on bioequivalence of orally inhaled drug products sponsored by the Product Quality Research Institute identified gaps in knowledge including: (1) cascade impactor studies are not a good predictor of the pulmonary dose and more detailed studies on *in vitro/in vivo* correlations are needed; (2) there is a lack of consensus on appropriate statistical methods for assessing *in vitro* results; (3) fully validated and standardized imaging methods might not be applicable due to problems of having access to radio-labeled innovator product; (4) if alternatives to current methods for establishing local delivery bioequivalence cannot be established, biomarkers (pharmacodynamic or clinical endpoints) with a sufficiently steep dose-response need to be identified and validated for all relevant drug classes; and (5) the utility of pharmacokinetic studies for evaluating "local pulmonary delivery" equivalence deserves more attention.[43] In light of these issues and "the cumulative list of unanswered questions," the workshop participants concluded "that at this time there is not a clear pathway for demonstration of bioequivalence of a generic DPI."[44]

BIPI shares that point of view and urges FDA to withhold approval of any proposed generic version of SPIRIVA unless and until these "unanswered questions" identified by the broader scientific community are fully resolved. Indeed, there is no question that the science in support of demonstrating bioequivalence of locally acting inhaled products is currently not at the same level as that for systemically absorbed oral products. Much more work is needed to (i) develop well-defined protocols with established endpoints for comparative clinical studies, (ii) develop and validate *in vitro-in vivo* correlations, and (iii) establish statistically justified criteria for declaring bioequivalence. At a minimum, BIPI respectfully urges FDA to address and resolve these questions before determining whether a proposed generic product is bioequivalent to SPIRIVA or any other BIPI Tiotropium Product.[45] And, in light of significant changes in

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[41] Adams, *supra* note 36, at 5 ("If, for example, a two-fold difference in dose cannot be detected for a reference ICS, then a generic product could deliver half as much or twice as much as the reference product without detection of the difference.").

[42] *See* Food & Drug Admin., *Approval Package for SPIRIVA, Clinical Pharamacology and Biopharmaceutics Review* 10, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-395.pdf_Spiriva_BioPharmr_P1.pdf.

[43] Adams, *supra* note 36, at 2.

[44] *Id.*

[45] FDA has previously concluded that is not required as a matter of law to issue a guidance document setting forth a methodology and approach to evaluating the bioequivalence of orally inhaled products prior to approving an ANDA. *See* Letter from Janet Woodcock, FDA, to Alan Bennett (Nov. 18, 2008), Docket No. FDA-2006-P-0073. Nonetheless, it is important to note that FDA has taken such prudent action previously for Nasal Aerosols. *See* Food & Drug Admin., *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action*, *supra* note 30. FDA published the first guidance on such issues in 1999 and invited public comment on that document (Docket No. 99D-1738). After reviewing those comments, and convening a meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee on Pharmaceutical Science

product behavior stemming from seemingly minor modifications to the formulation of SPIRIVA (as discussed *infra*),[46] and the potential for impact to the safety and efficacy profile compared to the RLD, BIPI requests that the agency not deviate from the requirement that any proposed generic version of SPIRIVA or any other BIPI Tiotropium Product must fully satisfy Q1/Q2 sameness requirements.[47]

(b) The Same Labeling Requirement

(i) Statutory and Regulatory Requirements

In addition to requiring a proposed generic product to be bioequivalent to the RLD, FDA may not approve an ANDA unless "the labeling proposed for the [generic] drug is the same as labeling approved for the [RLD] . . . ." 21 U.S.C. § 355(j)(4)(G). This requirement is essential because, as FDA has explained, "a generic drug product approved on the basis of studies conducted on the listed drug and whose labeling is inconsistent with the listed drug's labeling might not be considered safe and effective for use under the conditions prescribed, suggested, or recommended in the listed drug's labeling." 57 Fed. Reg. 17,950, 17,961 (Apr. 28, 1992). On the other hand, "[c]onsistent labeling will assure physicians, health professionals, and consumers that a generic drug is as safe and effective as its brand-name counterpart." *Id.* Thus, the same labeling requirement underpins the entire system of generic drugs because it ensures that physicians and patients have access to instructions for the safe and effective use of generic drugs.[48]

When Congress crafted this provision, it was careful to carve out only two very narrow exceptions from the requirement that a generic drug carry the same labeling as the RLD. 21 U.S.C. § 355(j)(4)(G).[49] The first of these exceptions is reserved for cases in which FDA has allowed a generic product to differ from the RLD in its active ingredient, strength, dosage form,

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in July 2001 to consider questions of particle size and particle size distribution, the agency substantially modified its original guidance and reissued the draft in 2003.

[46] *See, e.g., infra* Section II(B)(3)(b) (discussing changes to the excipient, lactose, and composition of the capsule).

[47] In 2007, FDA questioned whether Q1 and Q2 differences for inhalation products should be explored. *See* Food & Drug Admin., *Critical Path Opportunities for Generic Drugs* (May 1, 2007), *available at:* www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm#inhalation. But, even there, FDA acknowledged that such changes would require an analysis of the impact of chemical changes in the emitted aerosol, alteration of in vitro drug delivery due to changes in excipients, impact of formulation changes on local site (lung) safety, and whether changes in composition of liquid formulations modify the quality and quantity of leachable substances over the product's shelf life.

[48] As FDA declared in the context of promulgating new regulations for labeling, the "centerpiece for risk management for prescription drugs generally is the labeling which reflects thorough FDA review of the pertinent scientific evidence and communicates to healthcare practitioners the agency's formal, authoritative conclusions regarding the conditions under which the product can be used safely and effectively. FDA carefully controls the content of labeling for a prescription drug, because such labeling is FDA's principal tool for educating healthcare professionals about the risks and benefits of the approved product to help ensure safe and effective use." 71 Fed. Reg. 3922–3934 (Jan. 24, 2006).

[49] *See* § 355(j)(2)(A)(viii). A section viii statement is typically used when the brand's patent on the drug compound has expired and the brand holds patents on only some approved methods of using the drug. If the ANDA applicant follows this route, it will propose labeling for the generic drug that "carves out" from the brand's approved label the still-patented methods of use. See 21 CFR § 314.94(a)(8)(iv).

or route of administration. These changes are sufficiently substantial that they require an applicant to obtain FDA approval of a "suitability petition" before the generic manufacturer may even file an ANDA for the product. *See* 21 U.S.C. § 355(j)(2)(C). Absent any changes to the product, however, an ANDA applicant may not simply file a suitability petition to obtain approval of the generic product based on a different label or different instructions for use of its product. In fact, FDA expressly rejected that approach when it promulgated final regulations implementing the Hatch-Waxman Amendments.[50]

The only other exception to the same labeling requirement – the "different manufacturer exception" – is meant to accommodate exceedingly minor differences, such as address changes and differences in expiration dates, stemming from the fact that the generic drug product and RLD are produced or distributed by different manufacturers. The intent of Congress with respect to this exception is expressly set forth in the House Report accompanying the Hatch-Waxman Amendments. In pertinent part, it declares that

> An ANDA must contain adequate information to show that the proposed labeling for the generic drug is the same as that of the listed drug. The Committee recognizes that the proposed labeling for the generic drug may not be exactly the same. For example, the name and address of the manufacturers would vary as might the expiration dates of the two products. Another example is that one color is used in the coating of the listed drug and another is used in that of the generic drug. FDA might require the listed drug maker to specify the color in its label. The generic manufacturer, which has used a different color, would have to specify a different color in its label. H.R. Rep. No. 98-857, pt. 1, at pages 21-24.

FDA's regulations implementing the ANDA approval requirements also make clear that the different manufacturer exception is quite narrow and limited to trivial changes. In pertinent part, those regulations provide that "[d]ifferences between the applicant's proposed labeling and the labeling approved for the reference listed drug may include differences in expiration date, formulation, bioavailability, or pharmacokinetics, labeling revisions made to comply with current FDA labeling guidelines or other guidance, or omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(4)(D) of the act." 21 C.F.R. § 314.94(a)(8)(iv). Moreover, the preamble to these regulations makes clear that, beyond these exceptions, FDA sought to allow only for minor or trivial differences in the labeling of a generic product.[51] Hence, outside of these very limited and narrow exceptions, a proposed

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[50] In response to the proposed rule, one comment asked FDA to accept petitions to submit an ANDA for a product whose labeling differs from the reference listed drug. FDA rejected that comment, stating that "[s]uitability petitions are for drugs that have a different active ingredient, route of administration, dosage form, or strength. . . . Labeling differences, therefore, are not proper subjects for a suitability petition." *See* 57 Fed. Reg. 17,950 (Apr. 28, 1992).

[51] In the preamble accompanying FDA's proposed regulations, the agency emphasized that permissible differences in the labeling of a generic product are quite limited and, consistent with the above-referenced House Report, it provided the following additional examples of changes permitted under the manufacturer exception: " . . . (5) the name and address of the manufacturers of the proposed and listed drug products vary; (6) the expiration dates for the proposed product and the reference listed drug differ; (7) the National Drug Code (NDC) number for the proposed product and the reference listed drug differ, if displayed on the label and in the labeling; and (8) there are differences

generic version of SPIRIVA or any other BIPI Tiotropium Product must carry identical labeling.[52]

(ii) Application of the Same Labeling Requirement to Drug-Device Products

FDA has previously considered how the same labeling requirement applies specifically to the use of drug-device combination products such as SPIRIVA.[53] In response to two citizen petitions filed by King Pharmaceuticals, the agency outlined its approach to review and approval of such products under this provision.[54] There, FDA declared that, "with the exception of certain permissible differences due to difference in manufacturer," it will decline to approve a generic product if its labeling is not the same as the RLD. The agency indicated that "[c]ertain minor labeling changes may be acceptable to identify certain permissible differences between the ANDA and its RLD (*e.g.*, to identify a change in materials to make the product lighter or to make it more robust or durable), as are minor differences (such as cosmetic appearance, color, shape) between the RLD and ANDA labeling when they do not interfere with operating conditions." But, FDA also emphasized that "[d]esign differences are acceptable only if they do not significantly alter product performance or operating principles *and* do not result in impermissible differences in labeling."[55] (emphasis added)

At the same time, FDA stated that an ANDA for a generic drug-device product would not be approved if certain studies, including "clinical usability or human factor studies," are required to justify differences in a product and its labeling since "such studies are beyond the scope of studies that can be reviewed and approved in an ANDA." In support of that position, FDA indicated that certain changes in a drug-device product, such as a change in assembly, different operating principles, or different ergonomics, "may require further clinical data because potential clinical consequences might be unknown." Moreover, the agency recognized that there may be

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in the color used in a tablet (*e.g.*, the listed drug contains Yellow No. 5, which must be declared in the label, while the proposed product uses a different color)." 54 Fed. Reg. 28,872, 28,884 (July 10, 1989). *See also* 57 Fed. Reg. 17,950 (Apr. 28, 1992) (preamble accompanying final regulation adopts these examples).

[52] *See SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm., Inc.*, 211 F.3d 21, 27 n.2 (2d Cir. 2000) ("[T]the plain language of the Hatch-Waxman Amendments, their legislative history, and their interpretation by FDA all require manufacturers of generic drugs to copy the labeling of pioneer drugs "near-verbatim" to obtain ANDA approval."). *See also Biovail Corp v. FDA*, 519 F. Supp. 2d 39, 48 (D.D.C. 2007) ("Congress intended generic drug labels to provide the same information as the RLD.").

[53] FDA has previously indicated that inhalers are like prefilled syringes, insulin injector pens, and transdermal patches insofar as they constitute combination products where the components are physically, chemically, or otherwise combined. 21 C.F.R. § 3.2(e)(1) (2011). *See also* Food & Drug Admin., *Frequently Asked Questions About Combination Products*, http://www.fda.gov/CombinationProducts/AboutCombinationProducts/ucm101496.htm (last visited June 4, 2012).

[54] *See* Letter from Janet Woodcock, Director, CDER, to Thomas Rogers, King Pharmaceuticals (July 29, 2009) (Nos. FDA-2007-P-0128 and FDA-2009-P-0040) [hereinafter King Response] (granting in part and denying in part two citizen petitions filed by King Pharmaceuticals concerning FDA review of auto-injectors for sumatriptan succinate).

[55] In this context, FDA indicated that it would consider whether "any difference in materials, design, or operating principles introduces a new risk" — a determination that "includes consideration of both risks intrinsic to the new product and risks associated with switching from one product to the other without additional physician intervention or training." *Id.* at 6.

"instances where proper usage by a targeted patient population is in question" and additional studies such as "human factor analysis, actual use studies, and labeling comprehension studies may be warranted." Any of such studies would rule out approval of the product through an ANDA.[56]

Shortly following issuance of its response to the King petitions, FDA declined to grant a citizen petition filed by Dey Pharma L.P., requesting the agency to assign an "AB" rating to a generic auto-injector only if the color, shape, ergonomic characteristics, container, and needle protection mechanism of the generic product is the same as the RLD (in this case, EpiPen®).[57] FDA denied the Dey petition because it would "have the practical effect of categorically inhibiting any differentiation, however minor, between a generic and innovator epinephrine auto-injector product." The agency made clear, however, that it would carefully consider individual differences between auto-injectors (as well as the combined effect of those differences) on a case-by-case basis as they relate to safe and effective use of the product.

(iii) Application of the Same Labeling Requirement to DPIs

There are three principal types of DPIs: single-unit dose inhalers, multi-unit dose inhalers, and multi-dose reservoir inhalers.[58] The inhaler used with SPIRIVA (the HandiHaler) is an example of the first of these types of DPIs. As described previously, the drug is supplied in an individual gelatin capsule that is placed in the inhaler. When the patient depresses the plunger, the capsule is pierced and the patient then can inhale the powder from the punctured capsule. The spent capsule must be removed and discarded by the user. Multi-unit dose inhalers, on the other hand, utilize individually prepared and sealed doses of drug and, thus, dispense with the need for the patient to manually replace spent capsules or blisters. Generally, these DPIs require an action by the patient to slide the pre-packaged dose into place, where it is opened and ready for inhalation. Finally, multiple dose reservoir devices contain a bulk supply of drug from which individual doses are released. For such devices, the patient typically holds the inhaler vertically while actuating the device to release a dose of drug into a metering cup.

Given these different types of DPIs with markedly different designs and operating principles, there is no question that substantial confusion among patients would arise if FDA were to treat the different devices in these categories as interchangeable with one another for the

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[56] For products used without physician supervision and which require training of patients by a physician prior to initial unsupervised use, FDA considers whether patients can be safely switched to a new product without retraining by a physician or health care professional. As FDA indicated in its response to the King Petition, the key consideration becomes whether, in light of product differences, "patients can be safely switched to a new product without retraining by a physician or health care professional." *See* King Response, *supra* note 54, at 6. In the patient counseling section of the labeling for SPIRIVA, physicians are reminded of the importance "for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device." Physicians are directed to "[i]nstruct patients that SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications." In bold font, physicians are further instructed to "[r]emind patients that the contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed." *See SPIRIVA Label*, *supra* note 13, at 8.

[57] *See* Food & Drug Admin., No. 2009-P-0578, *Response to Dey Citizen Petition* (Nov. 30, 2009).

[58] *See* H. Chrystyn., *The Diskus: A Review of Its Position Among Dry Powder Inhaler Devices*, 61 Int'l J. Clinical Practice 883, 1022 (2007) (Exh. 9).

purposes of consideration of an ANDA.[59] The *Lee Paper* acknowledges this point and states that "a switch from one DPI to another . . . may cause confusion to the patient, resulting in incorrect use of the DPI device and ineffective disease treatment."[60] To avoid that problem, the article states that limiting approval of generic products to the same dose format (*i.e.*, pre-metered single dose, pre-metered multiple dose, or drug reservoir) as the RLD will help to ensure the effective use of the generic DPI product. BIPI strongly agrees with this recommendation and urges FDA to apply this requirement in connection with its consideration of any ANDA for SPIRIVA or any BIPI Tiotropium Product. Indeed, such a practice is mandated under the same labeling requirement since different DPIs will certainly carry different instructions for use.

Moreover, FDA must not just draw the line on possible substitution and interchangeability at these broad categories for DPIs. Indeed, as recognized at the *PQRI Workshop*, patients with significant experience with one inhaler may still have difficulty using a similar, but not identical, delivery system. Subtle differences in flow resistance, feel, taste, noise, and even appearance of two seemingly similar devices may influence their use, leading to differences in position, breathing patterns, total and regional drug delivery, and ultimately clinical effect. This patient-device interface is, of course, particularly important for DPIs, where the energy required for dispersion and delivery of the active moiety is dependent solely on patient inspiration. Any differences between two inhalers may be especially pronounced for a product such as SPIRIVA, which is approved to treat COPD patients who are generally older and have a degree of airflow obstruction.

FDA must also recognize that patients may still be compromised if they are switched to a generic product with the same dose format as the RLD. In fact, many inhalers with the same dose format are characterized by substantially different designs and operating principles, and are correspondingly accompanied by different instructions for use. The *Lee Paper* acknowledges this problem when it suggests that, notwithstanding the dose format, "any necessary deviation in the internal device design that significantly increases the complexity of product use for the patient . . . can compromise the interchangeability of test and reference DPI products in the patient's hands."[61] Accordingly, even for other single-unit DPIs, FDA must rigorously apply the same labeling requirement and principles articulated in the King Response to ensure the safety and efficacy of a generic version of SPIRIVA or a BIPI Tiotropium Product.[62]

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[59] As one investigator recently declared, "[d]ifferent inhaler types cause confusion and it is recommended that these should not be used interchangeably. Failure to consider these factors could result in a device misuse rate above 80%." *See* S. Wieshammer & J. Dreyhaupt, *Dry Powder Inhalers: Factors Associated with Device Misuse*, 1 Respiratory Drug Delivery Europe 95, 101 (2009) (Exh. 10). Other manufacturers have also acknowledged that patient confusion may result from use of an inhaler product that utilizes different technology than that which patients are accustomed. *See* Letter from J. Michael Nicholas, Teva, to FDA (June 16, 2010) (No. 2010-P-0317) ("[P]atients accustomed to one inhaler mechanism are likely to be confused when confronted by an improperly substituted inhaler mechanism that uses different technologies.").

[60] *See* Adams *supra* note 36, at 6.

[61] *See* Adams *supra* note 36, at 6–7.

[62] In this context, FDA must be especially careful to ensure that any proposed generic version of SPIRIVA does not impact a patient's eyes. Anticholinergic agents such as tiotropium may impact the ocular system so it will be important for FDA to ensure that patients are instructed effectively to avoid eye contact from improper handling of the inhaler or the container for the drug substance.

2. FDA Must Establish a Robust Clinical Program for Applications Referencing SPIRIVA or any other BIPI Tiotropium Product Under Section 505(b)(2)

(a) Applications for "Duplicates" of SPIRIVA May Not be Filed Under Section 505(b)(2) of the FDCA

Before turning to an analysis of the standards and requirements that should govern FDA's consideration of proposed follow-on versions of SPIRIVA or other BIPI Tiotropium Products, BIPI believes it is important for FDA to clarify precisely which types of tiotropium bromide products may be filed under Section 505(b)(2) in the first place. Indeed, while Congress created these two separate abbreviated pathways for approval of new drugs (*i.e.*, 505(j) and 505(b)(2)), FDA has made clear on numerous occasions that they may not be used interchangeably.

When FDA proposed regulations to implement the Hatch-Waxman Amendments, it declared that "[a]pplications for duplicates of listed drugs eligible for approval under ANDAs will be treated as submitted under section 505(j) of the act rather than under section 505(b) of the act, even if such applications are supported by literature reports of safety and effectiveness."[63] That requirement was thereafter embodied in FDA's final regulations, which provide that FDA may refuse to file an "application submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the act."[64] 21 C.F.R. § 314.101(d)(9). This requirement is also reflected in FDA's draft guidance for industry on applications covered by Section 505(b)(2). There, FDA declared that an application for a duplicate of a listed drug and eligible for approval under Section 505(j) may not be submitted as a 505(b)(2) application.[65]

Most recently, in response to a citizen petition filed by Mutual Pharmaceutical, Inc., FDA reiterated its position that applications for duplicate products must be filed under Section 505(j) of the FDCA.[66] The agency indicated that, "[a]s a matter of policy, the agency does not accept applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act." FDA also emphasized that the 505(b)(2) process is meant for products that differ from a listed drug and that duplicates will be treated as ANDAs "even if such applications are supported by literature reports of safety and effectiveness." In this context, FDA emphasized that the requirement that duplicate ANDA products have the same label as their RLDs "minimizes confusion among healthcare providers and potential safety risks to patients."

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[63] *See* Abbreviated New Drug Applications, 54 Fed. Reg. 28,872, 28,890 (proposed July 10, 1989).

[64] When FDA issued these regulations, it stated that "as a matter of policy, the agency does not accept applications under section 505(b)(2) of the act when there is a listed drug that would provide a basis for an application under section 505(j) of the act." *See* Abbreviated New Drug Applications, 57 Fed. Reg. 17,950, 17,956 (April 28, 1992). FDA has, however, indicated that, in addition, an applicant may submit a 505(b)(2) application for a change in a drug product that is eligible for consideration pursuant to a suitability petition under Section 505(j)(2)(C) of the Act.

[65] *See Draft 505(b)(2) Guidance, supra* note 22, at 6.

[66] *See* Letter from Janet Woodcock, FDA, to Gary L. Veron (May 25, 2011) (No. FDA-2010-P-0614) [hereinafter Colcrys Response].

FDA's longstanding policy of declining to consider duplicate products under Section 505(b)(2) is grounded in fundamental principles. As FDA recently declared,"[b]y generally requiring duplicate products to be marketed under section 505(j) of the FD&C Act, FDA also ensures that duplicate products are marketed with the same or similar labeling that FDA has determined contains the scientific information necessary for the safe and effective use of the drug product."[67] Moreover, this approach streamlines the drug approval process and ensures that applicants and FDA can rely to the greatest extent possible on what is already known about an approved drug product and avoid unnecessary duplication of human or animal studies. Finally, review of a duplicate product through an ANDA preserves the balance reached in the Hatch-Waxman Amendments. Indeed, if an applicant could avoid referencing a pharmaceutically equivalent product as its RLD by filing a 505(b)(2) application, it could circumvent the patent and exclusivity protection granted to the NDA holder and the 180-day exclusivity period granted to the first applicant for an ANDA.[68]

Thus, it is clear that an application for a "duplicate" product must be filed under Section 505(j) – not Section 505(b)(2) – of the FDCA.[69] Duplicate products are, in turn, pharmaceutical equivalents of the RLD. Indeed, in its Draft 505(b)(2) Guidance, FDA treats the term "duplicate" as synonymous with a pharmaceutical equivalent.[70] A duplicate product is, therefore, one that (among other things) contains identical amounts of the identical active drug ingredient in identical dosage forms as the RLD.[71] Most recently, in the context of considering whether an application for a particular product must be filed under Section 505(j) or Section 505(b)(2), the agency confirmed that "the informal term 'duplicate' generally refers to a drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug."[72]

Accordingly, on the basis of the foregoing analysis, an application for a duplicate of SPIRIVA or other BIPI Tiotropium Products must be submitted under Section 505(j), not Section 505(b)(2), and a "duplicate" of SPIRIVA includes any dry powder inhaler containing the

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[67] *See id.* at 13–14. Because there is no same-labeling requirement for a 505(b)(2) product, there is no mechanism by which to ensure that the 505(b)(2) product labeling would reflect relevant safety and efficacy information already acquired for the approved 505(b)(1) drug; under those circumstances, moreover, the 505(b)(2) and 505(b)(1) manufacturers could each continue to revise their respective product labels over time, leaving physicians and patients unsure as to which product information was accurate.

[68] *See* Food & Drug Admin., Docket No. 2004P-0386, *Response to Fenofibrate Citizen Petition* 9 n.13 (Nov. 30, 2004) (stating that an ANDA applicant seeking approval for a tablet dosage form should cite the approved tablet as its RLD and should not attempt to circumvent patents on the tablet dosage form by submitting a suitability petition that seeks to use an approved capsule as its RLD).

[69] FDA's regulations establish limited exceptions allowing certain products, which are duplicates of a listed drug, to be considered for approval under Section 505(b)(2) if, for example, the pharmacokinetic profile is intentionally different from the listed drug. *See* 21 C.F.R. § 314.54(b) (2011).

[70] *Draft 505(b)(2) Guidance*, *supra* note 22, at 11.

[71] 21 C.F.R. § 320.1(c) (2011). *See also Orange Book*, *supra* note 11, at vii (defining pharmaceutical equivalents as those that "contain the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration").

[72] *See* Colcrys Response *supra* note 66, at 12, n.38.

same amount of tiotropium bromide monohydrate as its sole active ingredient.[73] BIPI notes that, in the context of applying "pharmaceutical equivalence" to a drug delivery system such as a transdermal patch, FDA has indicated that it considers the amount of active ingredient to mean the amount that is "intended to furnish pharmacological activity or other direct effect" and not the amount of drug substance present in the delivery system to drive the delivery of the therapeutic dose.[74] Moreover, while the term "dosage form" is not specifically defined in the FDCA or its implementing regulations, FDA has indicated that a proposed drug product has the same dosage form as the RLD if it falls within the same dosage form category listed in Appendix C of the *Orange Book*."[75] Indeed, FDA has consistently made clear that it will consider products to be in the same dosage form even if they have different release mechanisms.[76] That is because the release mechanism is a part of the composition or formulation of the drug product, rather than the dosage form of the drug. 21 C.F.R. § 314.137(a)(8)(ii)(A).[77]

(b) FDA Should Require Robust Clinical Programs For Any Follow-on Product

As described previously, FDA has taken the position under Section 505(b)(2) that the agency may rely on its previous findings about the safety and efficacy of an RLD only to the extent that the proposed follow-on product shares common characteristics with the reference drug. Any differences must be evaluated with "bridging studies" to demonstrate that the changes will not adversely affect safety and effectiveness or otherwise undermine the applicability of FDA's findings.[78] As set forth below, BIPI's experience with oral inhalation products containing tiotropium bromide makes clear that even seemingly trivial differences in a follow-on product may have a significant impact on safety and efficacy. Thus, FDA must require any applicant for a follow-on version of SPIRIVA or any BIPI Tiotropium Product to conduct a robust and extensive clinical program to adequately characterize safety and efficacy in view of the specific characteristics of the RLD. Indeed, simple bridging studies, such as toxicology and pre-clinical

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[73] BIPI notes that FDA did approve ProAir® HFA, an albuterol metered dose inhaler, on October 29, 2004, under Section 505(b)(2) of the Act. The RLD for that application was PROVENTIL HFA. BI understands that the principal difference between these two products was the absence of the surfactant, oleic acid, from the proposed formulation of ProAir. Other differences included different ethanol concentrations and actuator orifice sizes (0.22 mm compared to 0.29 mm for PROVENTIL HFA).

[74] *See* Letter from Janet Woodcock, FDA, to Alexander Giaquinto, Schering-Plough (Aug. 30, 1996) (No. 95P-0242) [hereinafter Nitro-Dur Response].

[75] *See* Letter from Steven K. Galson, CDER, to Suzanne P. Rinne et al. 3 (Jan. 28, 2005) (Nos. 2004P-0506, 2004P-0472, 2004P-0540, 2004P-0340) [hereinafter Fentanyl Response]. FDA has indicated that this list is not binding on the agency, but it does provide guidance for industry on what constitutes the same dosage form. Appendix C of the *Orange Book* contains a list of 80 dosage forms that reflect FDA's characterization of the term as focused on appearance and method of administration.

[76] *See* Letter from Janet Woodcock, FDA, to Michael Halstead, Warner Chilcott (May 1, 2009) (No. 2008-P-0586) [hereinafter Doryx Response]. S*ee also Pfizer Inc. v. Shalala*, 1 F. Supp. 2d 38, 46 (D.D.C. 1998) ("a drug's dosage form is not based on its release mechanism but on its appearance and the way the drug was administered"), *rev'd on other grounds*, 182 F.3d 975 (D.C. Cir. 1999).

[77] Even if FDA considers a proposed generic version of an RLD with a different release mechanism to be in the same dosage form, the agency may decline to approve an ANDA if such differences render the proposed generic version unsafe or not bioequivalent to the RLD. *See* Fentanyl Response *supra* note 75, at 4 n.5.

[78] *See* King Response, *supra* note 54, at 4.

testing, will not be sufficient to assure the safety and efficacy of any follow-on product. Instead, FDA should require applicants to conduct extensive and robust clinical programs – that is, definitive and sufficiently powered efficacy and safety studies for the relevant endpoints – for any follow-on product.

(i) FDA's Longstanding Practice of Requiring Robust Clinical Programs for Changes Involving Orally Inhaled Products

The FDA has long recognized that modifications to an orally inhaled product may raise significant issues and, thus, clinical studies are needed to evaluate the safety and efficacy of such products. For example, in September 1994, the agency issued guidance clarifying the types of studies that should be conducted in connection with (among other things) replacing chlorofluorocarbon ("CFC") propellants used in MDIs.[79] There, FDA recommended that sponsors conduct a long term safety study of at least 200 patients for one year (or three hundred patients for six months and one hundred patients for one year) for changes involving a new formulation or device (*e.g.*, a switch from an MDI to DPI of the same drug). FDA also called for a dose ranging study and a minimum 12 week study with three arms (original formulation/device, new formulation/device, and placebo). The agency further stated that approval of additional indications for such modified products would require additional studies, as appropriate.[80] The requirements in these programs underscore the importance of a rigorous program to ensure the health and safety of patients. Following issuance of the 1994 Points to Consider guidance, sponsors seeking approval of formulation changes in MDIs to allow for a switch from a CFC propellant to a hydrofluoroalkane ("HFA") propellant have consistently conducted extensive clinical studies evaluating the safety and efficacy of such changes. All of these applications were submitted under Section 505(b) of the FDCA and entailed at least three pivotal safety and efficacy studies and at least one 12 month safety study. These products included VENTOLIN® HFA (2001), four pivotal studies, one 12 month safety study with 400+ patients; FLOVENT® HFA (2004), three pivotal studies, one 12 month safety study with 300+ patients; ATROVENT® HFA (2004), three pivotal studies, one 12 month safety study with 300+ patients;[81] XOPENEX® HFA® (2005),[82] three pivotal studies, one 12 month safety study with

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[79] *See* Food & Drug Admin., *Guidance for Industry, Points to Consider: Clinical Development Programs for MDI and DPI Drug Products* 3–8 (Sept. 1994), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071955.pdf.

[80] In this guidance, the only instance in which FDA did not call for a long term safety study to be conducted was where the change involved a switch from one approved device to another similar device with an identical formulation. In light of more recent information about such products and the diversity of different types of devices falling generally within the same category, BIPI believes that this recommendation is not sufficient to capture potential safety and efficacy issues for such changes.

[81] BIPI notes that, in connection with this NDA, several minor changes were made to the device (not the formulation) during the development program such that the product, which was ultimately approved for marketing, was not used in the pivotal phase 3 studies. To address that issue, FDA agreed that a single dose, dose-ranging using the device to be marketed would be acceptable in addition to a pharmacokinetic study. Moreover, FDA found that no new safety signals were noted in the clinical trials and that systemic exposure from the device to be marketed was lower than Atrovent CFC in COPD patients. *See* Food & Drug Admin., *Medical Review for Atrovent HFA, Application No. 21-5278, available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021527s000_MedR.pdf.

500+ patients; AEROSPAN™ HFA (2006), two pivotal studies, two 12-month safety studies with 400+ patients; and ADVAIR® HFA (2006), four pivotal studies, one 12-month safety study with 300+ patients.[83]

While recommending such studies for changes involving the formulation of MDIs, FDA has also acknowledged that DPIs may present more technical challenges for applicants than MDIs. Indeed, in an October 1998 draft guidance on chemistry, manufacturing and controls for MDIs and DPIs, the agency declared that the "wide array of DPI designs, many with characteristics unique to the design, will present challenges in developing information in support of an application."[84] This is especially the case since, as FDA emphasized, the dosing performance and therefore clinical efficacy of the product may be directly dependent on the design of the DPI. In light of these and other challenges, FDA indicated that changes in components of the drug product or changes in manufacturers should be carefully evaluated for safety, clinical effectiveness, and stability of the product. And the type and extent of scientific supportive information needed for such changes to DPIs could be more extensive than that needed for similar changes in more conventional drug products.

(ii) Specific Considerations Arising from BIPI's Experience with SPIRIVA

Given the importance of ensuring that patients have access to thoroughly vetted products whose risks and benefits have been adequately characterized and evaluated, FDA must require any 505(b)(2) application for a follow-on version of SPIRIVA or other BIPI Tiotropium Products to include a robust clinical program which ensures and effectively explores the safety and efficacy of such a product. Indeed, based on BIPI's substantial experience in developing SPIRIVA, it is clear from the data that even seemingly minor changes or differences may have a significant impact on the product and its safety and efficacy. At the same time, it is clear that, given the complexity and behavior of a product such as SPIRIVA, a follow-on applicant will need to conduct clinical studies for each indication and it may not extrapolate from one to the other. Several examples to illustrate these points follow below.

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[82] In this context, BIPI notes that FDA declined to allow the manufacturer of Xopenex to rely on two studies conducted with an early actuator design (and two studies conducted with spacers) to show evidence of the efficacy of levalbuterol. *See* Food & Drug Admin., *Medical Review for Xopenex HFA, Application No. 21-730* 26, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021730s000_MedR.pdf.

[83] FDA also required at least a 12 month safety study to support approval of other products that entailed changes from existing products. Examples include: Serevent Diskus (1997), Flovent Diskus (2000), and Advair Diskus (2000). *See* Food & Drug Admin., *Medical Review for Serevent Diskus Inhalation Powder, Application No. 20-692, available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphis See; t; Food & Drug Admin., *Medical Review for Flovent Diskus 50, Application No. 20-833, available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails; Food & Drug Admin., *Medical Review for Advair Diskus, Application No. 21-077, available at* http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphis t.

[84] *See CMC Guidance, supra* note 28, at 4.

FDA must be very careful to ensure that the quality of the particular excipients used in any follow-on version of SPIRIVA do not impact the safety and efficacy of the product. As described in the *Lee Paper*, due to the intrinsic cohesiveness and poor flow characteristics of small drug particles, an inert, coarse, soluble carrier is typically added to the dry powder formulation to facilitate dispersion, improve the powder flow and fluidization, and overcome problems related to dose metering and dose uniformity.[85] In this system, the fine drug particles adhere to the surface of carriers and these adhesive characteristics between the drug and carrier are important in determining the aerodynamic particle size distribution of aerosols and, hence, availability and distribution of the drug to the lungs. These adhesive forces can, in turn, be influenced by several factors, including the physiochemical properties of the drug and carrier, the drug-to-carrier ratio, the presence of other components, and process conditions.[86]

In SPIRIVA, lactose is utilized as the soluble carrier for the drug substance. In the course of utilizing this excipient, BIPI has found that lactose is critical to the performance of the product. Specifically, separate batches of SPIRIVA capsules were manufactured with either the defined and specified standard grade of lactose or with an "inhalation" grade of lactose from the same supplier. The *only* difference between the two grades of lactose was in the packaging: the packaging for the "inhalation" grade lactose was intended to provide a drier environment during storage. The particle size distributions of the SPIRIVA batches made with the two lactose grades fell within ±10% criteria, as did other key parameters. Yet, surprisingly, aerodynamic particle size distribution ("APSD") testing of the respective products did not yield similar results. While all batches made with the standard grade of lactose met APSD specifications, this was not the case for the batches made with the seemingly equivalent "inhalation" grade lactose. In fact, two thirds of the batches of drug product manufactured with the "inhalation" grade lactose fell outside of performance specifications. And, as illustrated below in *Figure 1*, both the total delivered dose and the fine particle dose showed significantly different patterns of behavior when the "inhalation" grade lactose was used.

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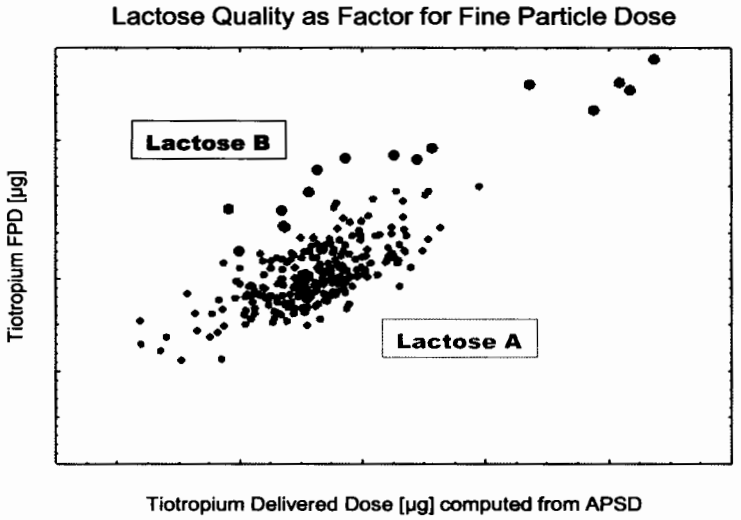
[85] *See* Adams, *supra* note 36, at 12.

[86] *See* D. Ganderton & NM Kassem, *Dry Powder Inhalers*, 6 J. Advanced Pharm. Sci. 165, 165–91(1992) (Exh. 11); *see also* J.N. Staniforth et al., *Interparticle Forces in Binary and Ternary Ordered Powder Mixes*, 34 J. Pharm. Pharmacology 141, 141–45 (1982) (Exh. 12).

Figure 1: Lactose Quality as a Factor for Fine Particle Dose[87]



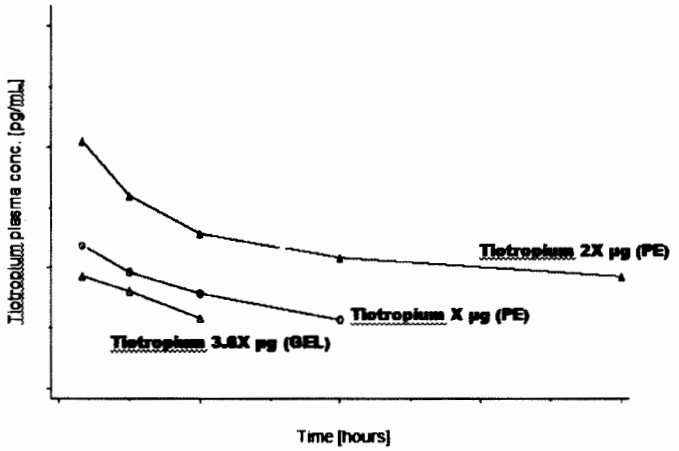
In its experience with SPIRIVA, BIPI has also found that a change in the composition of the capsule containing tiotropium bromide may result in different pharmacokinetic and pharmacodynamic profiles, even with seemingly appropriate adaptations to account for such differences. Specifically, during the development of an alternative delivery system for inhaled tiotropium bromide, BIPI utilized a modified HandiHaler and a capsule composed of polyethylene. The *in vitro* aerodynamic characteristics of this delivery system were matched to the original delivery system, where the capsule is formulated with gelatin and used in combination with the original HandiHaler. *In vitro* studies showed that the fine particle mass ("FPM," aerodynamic mass less than 5 µm) of tiotropium bromide in the gelatin capsule is about 3 µg at the nominal dose. To match that FPM, more than a 40% reduction in the nominal dose of the new capsule-inhaler system was necessary, indicating that seemingly minor changes to the capsule material and device resulted in a very significant alteration in nominal dose to match the fine particle mass of the original drug-device system.

Moreover, in an *in vivo* pharmacokinetic comparability study, the new formulation with the polyethylene capsule had a 1.65-fold higher peak plasma concentration and a 1.34-fold higher 12-hour systemic exposure than the original drug product. (*See Figure 2* below). This was the case despite the fact that the nominal dose of the new formulation was approximately 40% lower, the delivered dose was approximately 30% lower, and the new formulation had a comparable FPM. Furthermore, there was a distinct difference in pharmacodynamic response induced by the two delivery systems. In terms of lung function improvement as measured by FEV_1 $AUC_{0\text{-}12}$, there was a statistically significant difference of 21 mL ($p=0.02$) between the new and original formulations. This was unexpected given the match in FPM of those two formulations, and the differences indicate a different pharmacodynamic profile due to minor

[87] Identifying numbers have been redacted from the x- and y-axes of this figure to protect BIPI's trade secret information. Upon request from FDA, BIPI can provide an unredacted figure, which would not be subject to public disclosure under the Freedom of Information Act.

changes despite adaptations. Other important endpoints like symptomatic improvement and exacerbations could not be addressed in this Phase II study. Thus, seemingly minor modifications to an inhaled drug device combination can introduce unpredictable changes that significantly impact the overall performance of the product.

Figure 2: Gelatin to Polyethylene Capsule[88]



In addition, FDA will need to ensure that patients using any follow-on version of SPIRIVA avoid eye contact with tiotropium bromide since the agent may cause harm to the ocular system. Since a patient inserts a tiotropium bromide capsule into the HandiHaler, it will be particularly important to ensure that there is no powder on the exterior of the capsule that might end up getting into a patient's eyes. In the development program for SPIRIVA, BIPI carefully managed this issue through the design of powder filling equipment and the development of manufacturing data for the deposition of powder on the exterior surface of the capsule, as well as packaging conditions for the product that were gentle enough to avoid any breakage of capsules. Any DPI used with a follow-on product will need to be designed to avoid or minimize the potential for accidental exposure of tiotropium bromide to the eyes. This issue is of sufficient importance that BIPI, in connection with the SPIRIVA® RESPIMAT® (hereinafter "RESPIMAT") development program, conducted specific studies to evaluate potential substance exposure levels to the eyes in different possible misuse situations.

Finally, it should be emphasized that SPIRIVA capsules are moisture sensitive and, therefore, any container closure system used for a follow-on product would need to ensure adequate protection against moisture. This is especially critical because tiotropium bromide can undergo hydrolytic cleavage during product storage leading to a loss of the active ingredient (*Figure 3*). Similarly critical is the prevention of particle growth (agglomeration) due to moisture to ensure the consistency in aerodynamic fine particle mass (*Figure 4*). In the case of SPIRIVA, BIPI invested substantial time and resources in the development of two customized packaging systems for the tiotropium bromide capsules that balance the critical requirements for

[88] Identifying numbers have been redacted from this figure to protect BIPI's trade secret information. Upon request from FDA, BIPI can provide an unredacted figure, which would not be subject to public disclosure under the Freedom of Information Act.

optimum moisture protection with acceptable material for packaging and ease of handling by patients. These packaging and moisture control issues have been a major component of regulatory review of tiotropium bromide worldwide, and they should constitute a key element of any application seeking approval of a follow-on version of SPIRIVA.

Figure 3: Tiotropium Bromide Degradation as a Function of Initial Water Content[89]

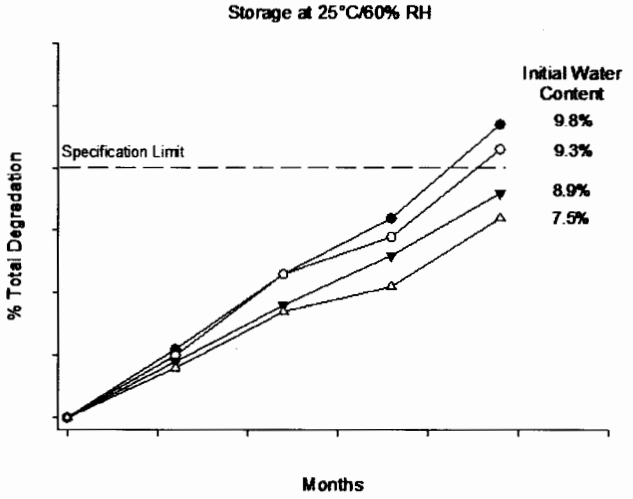
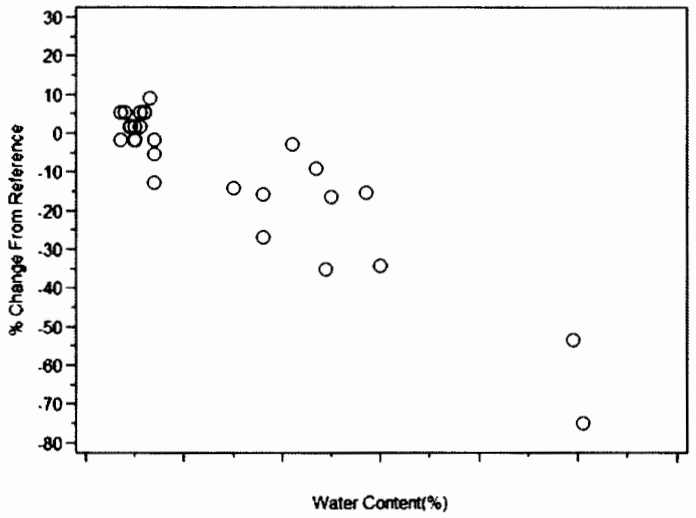


Figure 4: Moisture Sensitivity and Changes in Fine Particle Dose[90]



For its initial indication of maintenance treatment of bronchospasm associated with COPD, SPIRIVA was evaluated in clinical studies for improvement in lung function, as

[89] Identifying numbers have been redacted from this figure to protect BIPI's trade secret information. Upon request from FDA, BIPI can provide an unredacted figure, which would not be subject to public disclosure under the Freedom of Information Act.

[90] Identifying numbers have been redacted from this figure to protect BIPI's trade secret information. Upon request from FDA, BIPI can provide an unredacted figure, which would not be subject to public disclosure under the Freedom of Information Act.

measured by FEV1. For SPIRIVA's second indication of reducing COPD exacerbations, however, BIPI's clinical studies measured cough/sputum/wheezing/dypsnea/chest tightness with duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. BIPI was required to measure these different clinical outcomes in its exacerbation clinical studies. The same should be true of any follow-on product, particularly because it will by definition be different from, and not a duplicate of, SPIRIVA. To the extent that any applicant seeks approval of its follow-on product for exacerbations, it should be required to conduct equivalent clinical studies.[91]

(iii) Specific Considerations Arising From BIPI's Experience with RESPIMAT

In addition to the foregoing complexities surrounding seemingly minor changes to SPIRIVA, BIPI's experience with the development of RESPIMAT further underscores the cautious approach that FDA must adopt in connection with any 505(b)(2) application for a follow-on version of SPIRIVA or any other BIPI Tiotropium Product. Indeed, based on *in vitro* tests comparing SPIRIVA to RESPIMAT, the two products would be viewed as equivalent to each another in terms of *in vitro* respirable mass characteristics (*i.e.*, APSD) (*see Figure 5* below). Moreover, pharmacokinetic comparisons of the two formulations show that RESPIMAT (5 mcg) and SPIRIVA (18 mcg) have similar systemic exposure and urinary excretion.[92] (*see Figure 6* below). Yet, despite these findings, FDA has treated studies involving each product as not interchangeable or supportive of the other product. Thus, in connection with BIPI's efficacy supplement for use of SPIRIVA to treat exacerbations, FDA declined to rely on two one-year Phase III studies with RESPIMAT as supportive evidence. FDA declared that the results from combined analysis of clinical studies of RESPIMAT are not acceptable since these studies were conducted with RESPIMAT and not SPIRIVA – a distinct product in terms of efficacy.[93]

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[91] SPIRIVA's exacerbation indication is based on two studies – one of four years in duration and the other six months in duration. To the extent that a manufacturer of a follow-on version of SPIRIVA seeks approval for this indication, it should conduct equivalent studies.

[92] Food & Drug Admin., *Pulmonary-Allergy Drugs Advisory Committee Meeting for Spiriva HandiHaler (NDA 21-395): Clinical Briefing Document* 14 (Nov. 19, 2009), *available at* http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm190463.pdf. The nominal dose in RESPIMAT is different from SPIRIVA because of the differences in formulations and devices of the two products.

[93] *See* Food and Drug Admin., *Statistical Review and Evaluation for Spiriva HandiHaler (NDA 21-395): Clinical Studies* 6 (2009), *available at* http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm190463.pdf.

Figure 5: Aerodynamic Particle Size Comparisons of SPIRIVA and RESPIMAT[94]

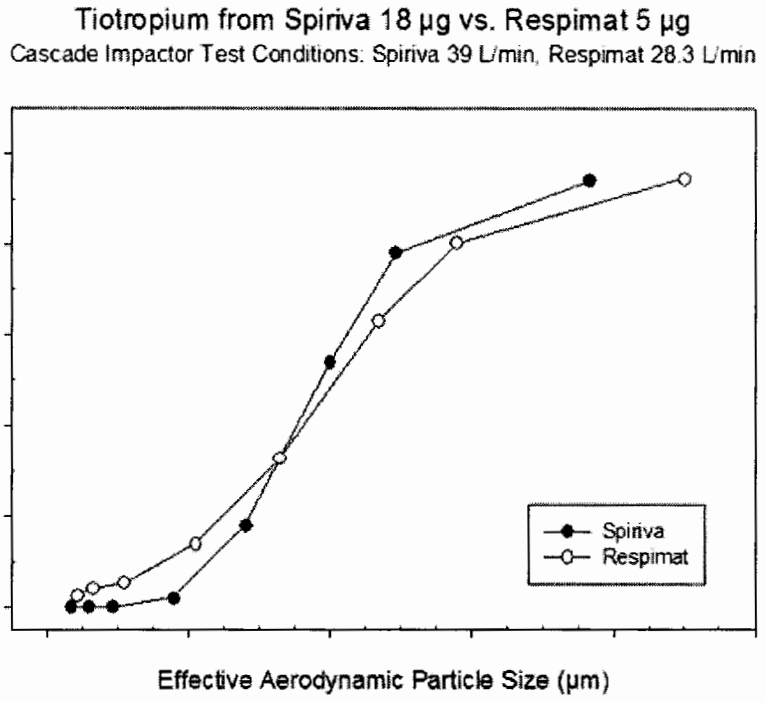
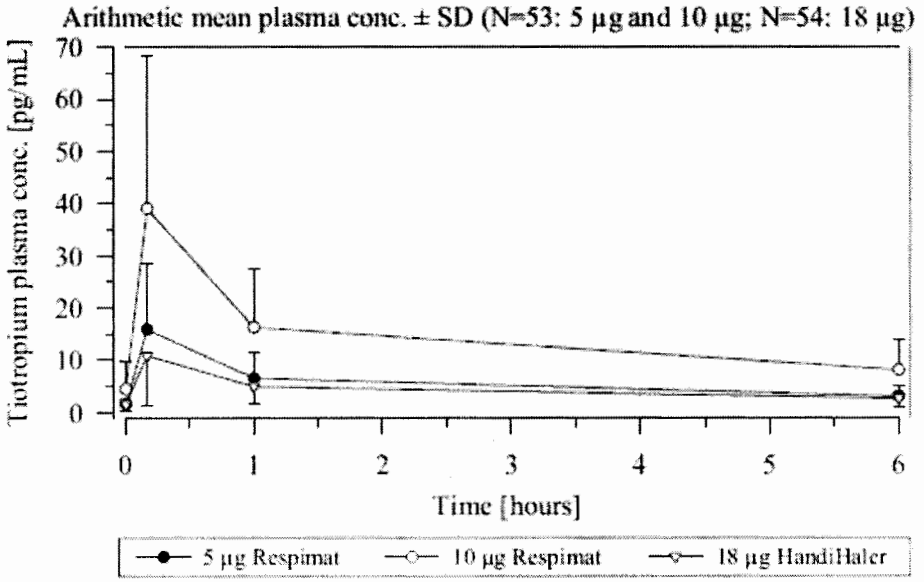


Figure 6: PK Comparison of SPIRIVA and RESPIMAT



BI Trial No.: 0205.0249

[94] Identifying numbers have been redacted from the x- and y-axes of this figure to protect BIPI's trade secret information. BIPI can provide an unredacted figure, subject to the Freedom of Information Act, to FDA upon request.

Thus, it is clear that FDA has been very careful not to rely on the findings for RESPIMAT to support conclusions about the efficacy of another tiotropium bromide product (SPIRIVA), even where the two products may appear comparable based on *in vitro* characterization tests.[95] Of course, FDA must apply the same approach to safety issues, and also require clinical studies to ensure that such issues have been fully resolved. Indeed, in connection with review of the NDA for RESPIMAT, BIPI informed the agency of an imbalance in fatal adverse events favoring the placebo group in one-year pivotal studies.[96] In response to that finding, FDA took the position that safety data from SPIRIVA trials may not be used in support of the safety of RESPIMAT and that these safety concerns must be addressed by data from an adequate and well-controlled study involving RESPIMAT. Given the potential that follow-on products may have safety results different from the RLD, BIPI believes that 505(b)(2) applicants should do more than the one year long safety study originally contemplated by FDA's 1994 non-binding "Points to Consider" Guidance.[97]

III. ENVIRONMENTAL IMPACT

This citizen petition qualifies for a categorical exemption from the requirement to submit an environmental assessment under 21 C.F.R. §§ 25.30(h) and 25.31(a).

IV. ECONOMIC IMPACT

Upon request by FDA, information regarding the economic impact of this proposal will be submitted to the agency.

V. CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: February 4, 2010 (publication of the PQRI Workshop

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[95] This approach is consistent with other pronouncements by FDA on the same question. FDA has, for example, previously declared that "[f]or inhalational pulmonary products, the FDA has generally considered efficacy to be primarily related to local effects. Therefore, efficacy data may not be directly transferrable from one device/formulation to another. Pharmacokinetic data in comparison with alternative formulations are useful as a benchmark but do not necessarily predict clinical dose ranging." Food & Drug Admin., *Pulmonary-Allergy Drugs Advisory Committee Meeting for Spiriva HandiHaler (NDA 21-395): Clinical Briefing Document*, *supra* note 92, at 13–14.

[96] Boehringer Ingelheim evaluated Spiriva RESPIMAT in two different doses (5 mcg and 10 mcg) in three, 48-week, double blind, placebo controlled, phase 3 clinical trials in patients with COPD. In all three trials, both 5 mcg and 10 mcg Spiriva RESPIMAT were statistically superior to placebo for trough FEV1 at 48 weeks. Food & Drug Admin., *Division Memorandum: Overview of the FDA Background Materials for an Efficacy Supplement for NDA #21-395 13* (Oct. 21, 2009), *available at* http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm190463.pdf.

[97] There is certainly precedent for FDA to depart from its earlier recommendations to require more of applicants based on safety concerns. *See, e.g.*, Colcrys Response, *supra* note 66, at 16.

entitled "Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPs): Workshop Summary Report") and March 31, 2011 (online publication of the PQRI Workshop entitled "Role of Pharmacokinetics in Establishing Bioequivalence for Orally Inhaled Drug Products: Workshop Summary Report"). If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: NONE. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

S. Luik

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Senior Vice President, Medicine and Regulatory
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VI. APPENDIX

Document	Exhibit
M Mannino et al., *Chronic Obstructive Pulmonary Disease Surveillance—United States, 1971-2000*, 51 MMWR Surveillance Summary SS-6, 1–8 (2002) [FN6]	1
Roberto Rodriguez-Roisin, *The Airway Pathophysiology of COPD: Implications for Treatment*, 2 J. COPD 253, 254 (2005) [FN8]	2
S. L. Lee. et al., *In Vitro Considerations to Support Bioequivalence of Locally Acting Drugs in Dry Powder Inhalers for Lung Diseases*, 2009 AAPS J. 414, 414 (2009) [FN31]	3
Wallace P. Adams, *The June 1999 Draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays: History, Recommendations and Local Delivery Issues* 9 (2001) [FN33]	4
Wallace P. Adams et al., *Demonstrating Bioequivalence of Locally Acting Orally Inhaled Drug Products (OIPS): Workshop Summary Report*, 23 J. Aerosol Med. Pulmonary Drug Delivery 1 (2010) [FN36 (1)]	5
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J. Mitchell et al., *In Vitro and In Vivo Aspects of Cascade Impactor Tests and Inhaler Performance: A Review*, 8 AAPS PharmSciTech 110, 110 (2007) [FN38]	7
P. T. Daley-Yates et al., *Pharmacokinetic, Pharmacodynamic, Efficacy, and Safety Data from Two Randomized, Double-Blind Studies in Patients with Asthma and an In Vitro Study Comparing Two Dry-Powder Inhalers Delivering a Combination of Salmeterol 50 μg and Fluticasone Propionate 250 μg: Implications for Establishing Bioequivalence of Inhaled Products*, 31 Clinical Therapeutics 370, 382–83 (2009) [FN39]	8
H. Chrystyn, *The Diskus: A Review of Its Position Among Dry Powder Inhaler Devices*, 61 Int'l J. Clinical Practice 883, 1022 (2007) [FN58]	9
S. Wieshammer & J. Dreyhaupt, *Dry Powder Inhalers: Factors Associated with Device Misuse*, 1 Respiratory Drug Delivery Europe 95, 101 (2009) [FN59]	10
D. Ganderton & NM Kassem, *Dry Powder Inhalers*, 6 J. Advanced Pharm. Sci. 165, 165–91(1992) [FN 86]	11
J.N. Staniforth et al., *Interparticle Forces in Binary and Ternary Ordered Powder Mixes*, 34 J. Pharm. Pharmacology 141, 141–45 (1982) [FN 86]	12