GlaxoSmithKline

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December 16, 2009

BY HAND DELIVERY

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

Dear Sir or Madam:

On behalf of GlaxoSmithKline, I herewith enclose a Citizen Petition requesting that specific legal and scientific requirements be upheld in the review of proposed generic copies of inhalation products containing fluticasone propionate and/or salmeterol xinafoate. I respectfully request the Food and Drug Administration to direct any correspondence relating to this petition to me at the above address and to counsel identified below:

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Thank you in advance.

Sincerely,

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GlaxoSmithKline

FDA-2009-P-0597-0001

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Citizen Petition of GlaxoSmithKline Requesting that Specific Legal and Scientific Requirements be Upheld in the Review of Proposed Generic Copies of Inhalation Products Containing Fluticasone Propionate and/or Salmeterol Xinafoate

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CITIZEN PETITION

I. INTRODUCTION AND ACTIONS REQUESTED

GlaxoSmithKline ("GSK") submits this Petition to request that the Food and Drug Administration ("FDA") take specific actions to uphold key public health and legal requirements in the review of proposed generic copies of oral inhalation products containing fluticasone propionate and/or salmeterol xinafoate (the "Inhalation Products").[1] Drug-device products with these active ingredients – including both metered-dose inhalers ("MDIs") and dry powder inhalers ("DPIs") – treat asthma and chronic obstructive pulmonary disease ("COPD"). These are serious respiratory conditions for which assurance of equivalent clinical outcomes with generic substitution is absolutely essential. GSK appreciates that in the balance between health care innovation and affordability, the availability of high quality follow-on products serves the public interest, as do appropriate protections and incentives for the research and development of the preceding pioneer products. *See, e.g.*, *Teva Pharmaceutical Industries Ltd. v. Crawford*, 410 F.3d 51 (D.C. Cir. 2005) (the Hatch-Waxman Amendments balance two key policy objectives: incentives for pharmaceutical innovation, and the timely availability of lower cost generic drugs). But the Inhalation Products are complex drug-device combination products, bearing quite distinctive performance characteristics and patient instructions for use and handling, and they raise serious questions about how to demonstrate bioequivalence reliably, as do respiratory products in general.

The public health and legal requirements on which this Petition is focused will assure that patients can make a seamless transition from use of an Inhalation Product to a substituted generic product without compromising safety and efficacy. With a therapeutic equivalence "A" rating that accompanies generic approval, mandatory or permissive substitution takes place at the pharmacy level without notification to patients and their prescribers, let alone their permission.[2] No special instructions or healthcare practitioner intervention of any kind accompany the substitution. Patients will literally be left to their own devices. It is under these "real world" conditions that FDA is called upon to fashion medically and legally appropriate approval standards. In the interest of public health, a scrupulous approach is warranted.

This Petition highlights two critical needs: (1) that patient instructions for use and handling of a generic copy of an Inhalation Product not deviate from instructions for the innovator product; and (2) that bioequivalence standards be adequate to assure equivalent clinical outcomes in the context of generic substitution.

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[1] The orally inhaled products GSK markets with one or both of these active ingredients are SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder), FLOVENT® DISKUS® (fluticasone propionate inhalation powder), FLOVENT® HFA (fluticasone propionate) Inhalation Aerosol, ADVAIR® DISKUS® (fluticasone propionate and salmeterol inhalation powder), and ADVAIR® HFA (fluticasone propionate and salmeterol) Inhalation Aerosol.

[2] As FDA has declared, "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." *See* FDA, *Approved Drug Products with Therapeutic Equivalence Evaluations* vii (29th Ed. 2009), *available at* http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf (hereafter the "*Orange Book*").

As for patient instructions, FDA recently recognized, in the closely analogous context of auto-injectors, that when training of patients is necessary to their successful unsupervised use of a drug-device combination product, the generic approval pathway is closed if a prospective generic copy requires different handling than the reference drug. Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research ("CDER"), FDA, to Thomas Rogers, King Pharmaceuticals (July 29, 2009), Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040 (granting in part and denying in part two citizen petitions filed by King Pharmaceuticals concerning FDA review of auto-injectors (hereafter "*King Response*") (Exh. 1). Likewise, senior FDA scientists with responsibility for approving innovator and generic respiratory products recently authored a paper noting concern about "confusion to the patient" and "ineffective disease treatment" that could result from different "operational techniques" between a substituted DPI and the reference product. Sau Lawrence Lee, *et al.*, *In Vitro Considerations to Support Bioequivalence of Locally Acting Drugs in Dry Powder Inhalers for Lung Diseases*, 11 AAPS J. 414 (2009) (hereafter "*Regulatory Note*" or "*Note*") (Exh. 2).[3] While studies to investigate the "real world" impact of such differences might be informative (studies of "actual use," "human factors," and the like), FDA confirmed in the auto-injector context that they are beyond the limits of investigations that can support Abbreviated New Drug Applications ("ANDAs") under Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the "FDCA"). *King Response*, at 7. The scientific literature, as will be discussed later, is already replete with reports of extensive misuse of inhalers, including when a new device has been substituted for one used differently, without any supervision. Because variability in the patient-device interaction can alter dose delivery and subsequent pharmacodynamic effects, the auto-injector precedent has full application here. Different instructions for how to use an inhaler properly – including priming, dosing, cleaning, and storing – are simply too significant to possibly fit into the very limited zone of labeling differences that the law permits for generic drugs.

As for bioequivalence, patients and prescribers increasingly are seeking reassurance of the reliability of FDA's determinations, and inhalation drug-device combination products are too complex, and too important in the maintenance treatment of serious conditions like asthma and COPD, to proceed without complete confidence. Dr. Janet Woodcock, Director of FDA's CDER, has reportedly acknowledged a "rising tide of skepticism" about the equivalence of generic drugs and innovator products.[4] In recent years, a number of professional medical societies have expressed concern about the transparency and adequacy of bioequivalence standards applied in different therapeutic areas.[5] Reports in the press echo these concerns and reflect public apprehension.[6]

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[3] GSK recognizes that the authors' views do not necessarily represent FDA's position.

[4] *See* James G. Dickenson, *Woodcock Cites Generic Skepticism as Priority*, Medical Marketing & Media (Jan. 1, 2009), *available at* http://www.allbusiness.com/pharmaceuticals-biotechnology/pharmaceutical/11761063-1.html (reporting on statements that Dr. Woodcock apparently made at a Generic Pharmaceutical Association conference in late 2008) (Exh. 3).

[5] *See, e.g.*, Peter R. Kowey, *Issues in Bioequivalence and Generic Substitution for Antiarrhythmic Drugs*, *available at* http://www.americanheart.org/presenter.jhtml?identifier-3015266 (last visited Sept. 25, 2009) (Exh. 4); Caroline Cassels, *AES Calls for Definitive Study to Examine Antiepileptic Drug Substitution*, Medscape Medical News (Dec. 3, 2007), *available at* http://www.medscape.com/viewarticle/566840 (Exh. 5); The Endocrine Society, *Position Statement on Bioequivalence of Sodium Levothyroxine* (2008), *available at* http://www.endo-society.org/advocacy/policy/upload/L-T4-Position-Statement-with-member-comments-header.pdf (Exh. 6); Letter

Careful attention is especially warranted in the realm of bioequivalence standards for the Inhalation Products. GSK has certain immediate concerns, and thus makes specific requests as noted below. GSK's more general plea, however, is that FDA continue methodically, consulting openly with experts in academia, members of industry, and other stakeholders, to develop broadly accepted data-driven standards for bioequivalence. GSK appreciates that a deliberative process is now underway, and that a multi-faceted framework can be anticipated. GSK acknowledges, in particular, that FDA scientists have recently published in the field,[7] and have been sponsoring clinical studies and participating in public meetings airing the issues.[8] GSK employees have also been among the speakers and organizers of past and upcoming public workshops, and looks forward to continued active participation in these formative scientific and regulatory deliberations.

For its specific requested actions, GSK requests that FDA not approve any ANDA referencing an Inhalation Product unless the proposed generic copy:

(1) conforms to the reference listed drug ("RLD") in its patient instructions for use and handling, as any differences are likely to lead to confusion among patients, particularly the elderly and pediatric populations;

(2) conforms to the RLD in its formulation according to prevailing qualitative/quantitative sameness standards ("Q1/Q2"), as part of the demonstration of bioequivalence;

(3) has been successfully clinically tested in both pediatric and adult patients, as part of the demonstration of bioequivalence, as extrapolation of results from one population to the other is not scientifically appropriate; and

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from Donald M. Poretz, MD, President, Infectious Diseases Society of America, to Dr. Janet Woodcock, Acting Director, CDER, FDA (Nov. 14, 2007) (commenting on FDA's decision to rely only on *in vitro* data in making bioequivalence determinations for vancomycin products that act locally in the gastrointestinal tract), *available at* http://www.viropharma.com/About%20Us/~/media/Files/July_2008_Advisory_Committee_Comments.ashx (Exh. 7).

[6] *See, e.g.,* Melinda Beck, *Inexact Copies: How Generics Differ From Brand Names*, Wall Street Journal, Apr. 22, 2008, *available at* http://online.wsj.com/article/SB120882069010332969.html (Exh. 8). The drug product Wellbutrin XL (bupropion hydrochloride extended-release tablets) and its generic copies are featured in this report. Earlier this year GSK divested US commercial rights and transferred ownership of the new drug application for Wellbutrin XL back to Biovail, which had developed the formulation. GSK continues to market the product elsewhere in the world.

[7] *See, e.g., Regulatory Note*; and C. Guo, *et al., Evaluation of Impaction Force of Nasal Sprays and Metered-Dose Inhalers Using the Texture Analyser*, AAPS J., 5-6 (2009) (published online June 3, 2009) (Exh. 9).

[8] For instance, at a meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology on July 23, 2008, FDA scientists reviewed plans to commission research to explore potential alternative approaches to assessing bioequivalence for inhaled corticosteroids (hereafter the "*FDA AdCom*"). As well, Agency representatives took part in planning and were among attendees at a meeting that the Product Quality Research Institute ("PQRI") convened on March 9 and 10, 2009 (hereafter the "*PQRI Meeting*"), to address, in the words of the workshop brochure, "scientific considerations for demonstrating bioequivalence that may be considered in the development of locally acting orally inhaled drug products and in the preparation of regulatory guidances for NDAs, ANDAs, and post-approval changes." PQRI Meeting Objective and Agenda, *available at* http://www.pqri.org/workshops/Bioequiv/imagespdfs/confinfo/Workshop_Final_Agenda.pdf (Exh. 10). A follow-up workshop is planned for next year.

(4) has been successfully clinically tested in both asthma and COPD patients as part of the demonstration of bioequivalence, as extrapolation of results from one disease state to the other is not scientifically appropriate.

The detailed scientific and legal grounds for these requests are set forth below.

II. STATEMENT OF GROUNDS

A. Background – The Disease States and Inhalation Products at Issue

1. Asthma and Chronic Obstructive Pulmonary Disease and Their Significant Burden of Disease

Although asthma outcomes have improved over the past decade, the burden of this disease remains substantial. Asthma is estimated to affect 300 million individuals worldwide, including 22 million in the U.S., and is responsible for approximately 250,000 worldwide deaths annually with approximately 3,600 of them in the U.S. in 2006.[9] It affects the old and the young, and claimed approximately 13 million lost school days and 10 million lost work days in 2003.[10]

COPD is the fourth-leading cause of death in the United States.[11] Approximately 24 million Americans have COPD, of whom 12 million are undiagnosed.[12] The age-adjusted death rate from COPD-related causes continues to increase while deaths from the other major killers such as coronary artery disease and stroke are decreasing.[13] The mortality rate in women now exceeds that in men.[14] COPD most often strikes individuals over the age of 40 who have a history of smoking.[15] Because of the cumulative effects of smoking in susceptible individuals, a

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[9] American Lung Association, Epidemiology & Statistics Unit, Research And Program Services Division, *Trends in Asthma Morbidity and Mortality* (2009), *available at* www.lungusa.org (Exh. 11); Melonie Heron, *et al.*, *Deaths: Final Data for 2006*, 57 National Vital Statistics Report 14 (2009) (Exh. 12); National Asthma Education and Prevention Program, National Institutes of Health, *The NAEPP Expert Panel Report 3 (EPR-3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma* (2007), *available at* http://www.nhlbi.nih.gov/guidelines/asthma/asthsumm.pdf (Exh. 13); Global Initiative for Asthma, *Global Strategy for Asthma Management and Prevention* (2008), *available at* http://www.ginasthma.org/Guidelineitem.asp??l1=2&l2=1&intId=1561 (Exh. 14).

[10] American Lung Association, Epidemiology & Statistics Unit, Research And Program Services Division, *supra* n. 9.

[11] American Lung Association, *Trends in Chronic Bronchitis and Emphysema: Morbidity and Mortality* (2009) (Exh. 15).

[12] *Id.*; David M. Mannino, *et al.*, *Chronic Obstructive Pulmonary Disease Surveillance – United States, 1971-2000*, 47 Respiratory Care 1184 (2002) (Exh. 16); National Institutes of Health, National Heart, Lung, and Blood Institute, *Morbidity and Mortality: 2007 Chart Book on Cardiovascular, Lung, and Blood Diseases* (2007), *available at* http://www.nhlbi.nih.gov/resources/docs/07-chtbk.pdf (Exh. 17).

[13] American Lung Association, *supra* n. 11.

[14] *Id.*

[15] Global Initiative for Chronic Obstructive Lung Disease, *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease* (2008), *available at* http://www.goldcopd.org/Guidelineitem.asp?l1=2&l2=1&intId=2003 (Exh. 18).

greater proportion of elderly patients with COPD are likely to have more severe disease than younger age groups.[16]

There are clear pathophysiological differences between COPD and asthma. With asthma, the pathophysiology is defined by airway inflammation and smooth muscle dysfunction.[17] The muscles of the bronchial walls tighten and cells in the lungs produce extra mucus, further narrowing the airways.[18] This can cause symptoms like shortness of breath, wheezing, coughing, and chest tightness, which are a result of increased resistance to expiratory flow due to airway inflammation, narrowing of airways due to smooth muscle contraction, and partial or total blockage of airway segments due to mucus plugs.[19] In some cases, breathing may be so labored that an asthma attack becomes life-threatening.[20]

The pathophysiology of COPD, by contrast, is defined by "airflow limitation that is not fully reversible."[21] This limitation is usually progressive and "is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking."[22] COPD is a multi-component disease encompassing airflow limitation, mucociliary dysfunction, structural changes, and inflammation.[23] COPD is a systemic disease that often includes poor nutritional status, reduced body mass index, and impaired skeletal muscle weakness and wasting.[24] The inflammation in COPD is characterized by an increase in neutrophils, macrophages, and T-lymphocytes (specifically CD8+) in various parts of the lungs, which relate to the degree of airflow limitation.[25] Eosinophils may also increase in some patients, particularly during exacerbations.[26] This inflammation pattern in COPD is markedly different from that seen in patients with asthma.[27]

Not only are there distinct pathophysiological differences between COPD and asthma, but those pathophysiological differences can have an effect on the deposition of drug in the lungs of these different types of patients. One research center conducted essentially sister studies of

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[16] Charles Fletcher and Richard Peto, *The Natural History of Chronic Airflow Obstruction*, 1 Brit. Med. J. 1645 (1977) (Exh. 19).

[17] National Asthma Education and Prevention Program, National Institutes of Health, *supra* n. 9.

[18] *Id.*

[19] *Id.*

[20] *Id.*

[21] B.R. Celli and W. MacNee, *Standards for the Diagnosis and Treatment of Patients with COPD: A Summary of the ATS/ERS Position Paper*, 23 Eur. Respiratory J. 932, 933 (2004) (Exh. 20).

[22] *Id.*

[23] Roberto Rodriguez-Roisin, *The Airway Pathophysiology of COPD: Implications for Treatment*, 2 J. COPD 253 (2005) (Exh. 21).

[24] Global Initiative for Chronic Obstructive Lung Disease, *supra* n. 15.

[25] American Thoracic Society and European Respiratory Society, *Standards for the Diagnosis and Management of Patients with COPD* (2004), *available at* www.thoracic.org/go/copd (Exh. 22).

[26] *Id.*

[27] Celli and MacNee, *supra* n. 21.

inhaled fluticasone propionate with the same design, matching healthy subjects as controls against asthmatics in one study and against COPD patients in the other.[28] The asthmatics and COPD patients had comparable lung function and the respective control groups were similar demographically. The findings demonstrated that the absolute bioavailability of fluticasone propionate was approximately 30% lower in asthmatics than in COPD patients.[29]

2. GSK's Portfolio of Inhalation Products for the Maintenance Treatment of Asthma and Chronic Obstructive Pulmonary Disease

As previously noted, the Inhalation Products contain either salmeterol xinafoate ("SAL"), fluticasone propionate ("FP"), or both. SAL is a long-acting beta-adrenergic receptor agonist that relaxes and opens air passages in the lungs. FP is a corticosteroid that treats inflammation of the airways.

GSK has developed and currently markets five Inhalation Products containing these active drug substances: SEREVENT® DISKUS® (salmeterol xinafoate inhalation powder), FLOVENT® DISKUS® (fluticasone propionate inhalation powder), FLOVENT® HFA (fluticasone propionate) Inhalation Aerosol, ADVAIR® DISKUS® (fluticasone propionate and salmeterol inhalation powder), and ADVAIR® HFA (fluticasone propionate and salmeterol) Inhalation Aerosol.

For the DISKUS products, the active ingredients are formulated in an inhalation powder and delivered via a DPI housing a blister strip carrying multiple pre-metered doses. For the HFA products, the active ingredients are formulated as an inhalation aerosol and delivered via an MDI.[30]

Further details of the Inhalation Products – application numbers, approved uses, detailed product descriptions, and approval dates – are recited in the table below.

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[28] Martin H. Brutsche, *et al.*, *Pharmacokinetics and Systemic Effects of Inhaled Fluticasone Propionate are Different in Asthmatics and Normal Volunteers*, 356 Lancet 556 (2000) (Exh. 23); S.D. Singh, *et al.*, *Pharmacokinetics and Systemic Effects of Inhaled Fluticasone Propionate in Chronic Obstructive Pulmonary Disease*, 55 Brit. J. Clinical Pharmacology 375 (2003) (Exh. 24).

[29] *See* Brutsche, *et al.*, *supra* n. 28 (finding the absolute bioavailability of fluticasone propionate in asthmatics to be 10.1% (95% CI 7.9, 14.0) versus 21.4% in healthy subjects (95% CI 15.4, 32.2)); and S.D. Singh, *et al.*, *supra* n. 28 (finding the absolute bioavailability of fluticasone propionate in COPD patients to be 13.3% (95% CI 9.0, 19.8) and 21% (95% CI 13.4, 33.0) in healthy patients). Thus, bioavailability was 53% lower in asthmatics compared to healthy subjects versus 37% lower in COPD patients compared to healthy subjects, which translates to an approximate 30% difference between asthma and COPD bioavailability.

[30] FDA has designated powder inhalation as the dosage form for GSK's DISKUS products. The agency has indicated that the dosage form for the MDI products is aerosol metered inhalation. *See Orange Book*, *supra* n. 2.

PRODUCT NAME	APPROVED USES AND DESCRIPTION OF PRODUCT	NEW DRUG APPLICATION ("NDA") #	DATE FIRST APPROVED
SEREVENT DISKUS[31]	Approved for asthma (including in pediatric patients ≥ 4 years old) and COPD SAL inhalation powder; 50 mcg per blister (labeled 50 mcg of salmeterol base is equivalent to 72.5 mcg of salmeterol xinafoate salt), with each device containing 60 or 28 blisters	20-692	Sept. 19, 1997[32]
FLOVENT DISKUS[33]	Approved for asthma (including in pediatric patients ≥ 4 years old) FP inhalation powder; 50, 100, or 250 mcg per blister, with each device containing 60 or 28 blisters	20-833	Sept. 29, 2000[34]
FLOVENT HFA[35]	Approved for asthma (including in pediatric patients ≥ 4 years old) FP inhalation aerosol; 44, 110, or 220 mcg per actuation, ex-actuator, with each canister intended for 120 actuations	21-433	May 14, 2004 Oct. 25, 2006 (with dose-counter)

[31] SEREVENT DISKUS FDA-approved labeling (Exh. 25).

[32] SAL was originally approved for use in the treatment of asthma in a chlorofluorocarbon-containing MDI ("CFC-MDI") on February 4, 1994. Consistent with the Montreal Protocol and the resulting phase out of CFCs, GSK elected to discontinue salmeterol CFC-MDI in the United States in 2002 as part of the process of removing all CFC-containing products from the marketplace.

[33] FLOVENT DISKUS FDA-approved labeling (Exh. 26).

[34] FP was first approved for use in the treatment of asthma as a CFC-MDI on March 27, 1996. As with the CFC-MDI containing SAL, GSK discontinued marketing of FP CFC-MDI in the United States in 2005 in connection with the phase out of CFCs under the Montreal Protocol.

[35] FLOVENT HFA FDA-approved labeling (Exh. 27).

PRODUCT NAME	APPROVED USES AND DESCRIPTION OF PRODUCT	NEW DRUG APPLICATION ("NDA") #	DATE FIRST APPROVED
ADVAIR DISKUS[36]	Approved for asthma (including in pediatric patients ≥ 4 years old) and COPD (250/50 mcg strength only) FP/SAL inhalation powder; 100/50, 250/50, or 500/50 mcg per blister (labeled 50 mcg of salmeterol base is equivalent to 72.5 mcg of salmeterol xinafoate salt), with each device containing 60, 28, or 14 blisters	21-077	Aug. 24, 2000
ADVAIR HFA[37]	Approved for asthma (including in pediatric patients ≥ 12 years old) FP/SAL inhalation aerosol; 45/21, 115/21, or 230/21 mcg per actuation, ex-actuator (labeled 21 mcg of salmeterol base is equivalent to 30.45 mcg of salmeterol xinafoate salt), with each canister intended for 60 or 120 actuations	21-254	June 8, 2006 July 31, 2008 (with dose-counter)

3. Patient Training and Instructions for Using the Inhalation Products

Correct use of inhalation products, including the Inhalation Products, is sufficiently complex and important to require healthcare professional training of patients prior to initial use and provision of detailed narrative and graphic instructions to patients.

For example, each of the Medication Guides for ADVAIR DISKUS, ADVAIR HFA, and SEREVENT DISKUS clearly directs the patient not to use the product "unless your healthcare provider has taught you and you understand everything."[38] The direction to have healthcare professional training and instruction prior to using the products is reiterated with respect to children using those devices: "children should use [product name] with an adult's help, as instructed by the child's healthcare provider."[39] Likewise, the Patient's Instructions for Use of

[36] ADVAIR DISKUS FDA-approved labeling (Exh. 28).

[37] ADVAIR HFA FDA-approved labeling (Exh. 29).

[38] SEREVENT DISKUS labeling, *supra* n. 31; ADVAIR DISKUS labeling, *supra* n. 36; and ADVAIR HFA labeling, *supra* n. 37. The FLOVENT products' labeling does not include this exact language because it does not include a Medication Guide. For purposes of the "same labeling" issues raised in this Petition, however, there is no reason for FDA to distinguish between FLOVENT and the other Inhalation Products.

[39] *Id.* (only the DISKUS products, indicated for pediatric patients as young as four years old, carry this advisory).

FLOVENT DISKUS (and FLOVENT HFA) states that "[c]hildren should use FLOVENT DISKUS under adult supervision, as instructed by the patient's doctor."[40]

FDA expects orally inhaled products to carry "detailed, step-by-step, appropriately illustrated instructions for patient use,"[41] and the Inhalation Products meet this standard. The instructions include not only precise directions for the inhalation maneuver, but also proper storage, priming, and cleaning. Graphic illustrations of the precise dosing maneuvers required of patients are part of the instructions.[42]

B. A Proposed Generic Copy Cannot Deviate from the Reference Inhalation Product in Its Patient Instructions for Use

1. The Legal Requirement of "Same Labeling" for ANDA Approval

Section 505(j)(4)(G) of the FDCA mandates, with limited exceptions not applicable here (though addressed below), that a generic product carry the same labeling as the RLD. That provision precludes FDA from approving an ANDA for a generic drug product if:

> information submitted in the application is insufficient to show that the labeling proposed for the [generic] drug is the same as labeling approved for the ... [RLD] except for changes required because of differences approved under a [suitability] petition filed under paragraph (2)(C) or because the [generic] drug and the ... [RLD] are produced or distributed by different manufacturers.

21 U.S.C. § 355(j)(4)(G). The same labeling requirement is critical 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. 17950, 17961 (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, as the Court of Appeals for the Second Circuit declared, "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." *SmithKline Beecham Consumer Healthcare, L.P. v. Watson Pharm., Inc.*, 211 F.3d 21, 27, n. 2 (2nd Cir. 2000); *see*

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[40] FLOVENT DISKUS labeling, *supra* n. 33 (only FLOVENT DISKUS is indicated for pediatric patients as young as four years old).

[41] FDA set forth this expectation for both DPIs and MDIs in its 1998 draft guidance document outlining necessary documentation for these products. *See* FDA, *Draft Guidance for Industry, Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products, Chemistry, Manufacturing and Controls Documentation* (1998) (hereafter "*Draft CMC Guidance*"), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070573.pdf.

[42] *See, e.g.*, labeling for SEREVENT DISKUS, *supra* n. 31, ADVAIR DISKUS, *supra* n. 36, and ADVAIR HFA, *supra* n. 37.

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.").

a. Permitted Labeling Differences are Minor and Exclude Differences in Dosing and Handling Instructions

When Congress crafted the "same labeling" provision, it was careful to carve out only two narrow exceptions. Neither applies here.

The first of these exceptions is reserved for cases in which FDA has allowed – via prior approval of a suitability petition – a generic product to differ from the RLD in its active ingredient, strength, dosage form, or route of administration. 21 U.S.C. § 355(j)(2)(C). Labeling differences permitted under this exception are strictly limited to those necessary to reflect differences approved in the petition. 21 U.S.C. § 355(j)(4)(G). No suitability petition is contemplated in the case of the Inhalation Products.[43]

The only other exception – the so-called "different manufacturer exception" – does not permit any differences, such as deviations in patient instructions for use, that would compromise the safety or efficacy of the product. It was meant to accommodate only insignificant differences attributable to alternative sourcing of a product, such as expiration dates, listings of inactive ingredients, and addresses (for places of business). Congressional intent could not be more clear:

> 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 [the House Committee reporting on legislation that culminated in the Hatch-Waxman Amendments] 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 22 (1984).

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[43] Within the category of DPI or MDI, the dosage form would remain constant even as device appearance, design, and function – and associated instructions for patient dosing and handling – may vary. *See, e.g.*, Letter from Steven Galson, Acting Director, CDER, FDA, to Susan Rinne, Vice-President, Alza Corporation, *et al.* (Jan. 28, 2005), Docket Nos. 2004P-0506/CP1, 2004P-0472/CP1, 2004P-0540/CP1, and 2004P-0340/CP1 (denying citizen petitions of Alza and others concerning FDA approval of generic versions of fentanyl transdermal systems) (Exh. 30). There, FDA stated that it has consistently chosen not to base its dosage form descriptions on release mechanisms and technologies. As an example of that policy, FDA stated that "drug products classified under the dosage form 'spray' may vary in the type of container closure system used, the actuator, or the nozzle, yet FDA considers all sprays to be the same dosage form in spite of differences in release technologies."

The preamble accompanying FDA's proposed regulations implementing the "different manufacturer" exception "emphasizes that *the exceptions* to the requirement that a generic drug's labeling be the same as that of the listed drug *are limited*." 54 Fed. Reg. 28872, 28884 (July 10, 1989) (emphases added). Consistent with the House Report quoted above, FDA gave several examples of the kind of limited labeling variations that would be permissible:

> (1) the method of formulation (e.g., inactive ingredients) differs; (2) the applicant's product and the reference listed drug have different strengths (in the case of petition-approved drug products) or with respect to the "how supplied" section of the labeling, the generic manufacturer does not supply all strengths of the drug product; (3) the reference listed drug labeling does not reflect current agency labeling standards; for example, the agency may require a change in the labeling of a drug product to make available important new information about the safe use of a drug product, but the reference listed drug's labeling has not yet been updated to reflect this change; (4) the reference listed drug labeling includes conditions of use that are protected by a patent or are accorded a period of exclusive marketing; (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 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).

Id. Language for the labeling regulations was proposed to accommodate these kinds of limited differences. *Id.* at 28923. The language of the final regulations is consistent. 57 Fed. Reg. at 17953 ("In the preamble to the proposed rule, the agency described various types of labeling differences that might fall within the permitted exceptions. . . . The agency will carefully review all differences annotated by the applicant in determining if such differences fall within the limited exceptions permitted by the act.").

The accumulated case law further reinforces the very limited scope of the "same manufacturer" exception. In *Zeneca, Inc. v. Shalala*, 213 F.3d 161 (4th Cir. 2000), the Court of Appeals for the 4th Circuit did uphold FDA's decision allowing a generic drug to include different labeling than the RLD. Those changes, however, which included specification of a different preservative and associated warnings about its allergenic effects, were found by the court to "fit squarely" within the precise language of FDA's regulations allowing for formulation differences and requiring sulfite warnings. 21 C.F.R. § 314.94(a)(8)(iv) ("Such differences between the applicant's proposed labeling and labeling approved for the reference listed drug may include differences in . . . formulation"); 21 C.F.R. § 201.22(b). Nothing in FDA's regulations implementing the different manufacturer exception, however, provides for variations in instructions for patient use and handling.

One particular aspect of the "different manufacturer" exception highlights the impermissibility of labeling variations between a generic copy and its RLD that could compromise safe and effective product use. FDA has taken the position, in implementing the "different manufacturer" exception in conjunction with the FDCA's exclusivity and patent provisions, that the labeling of a generic product may omit "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). The courts have upheld FDA's interpretation. *Bristol-Myers Squibb Co. v. Shalala*, 91 F.3d 1493 (D.C. Cir. 1996); *Sigma-Tau Pharm. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002). FDA, however, unequivocally draws the line at any so-called labeling "carve outs" that would "render the proposed generic drug product less safe and effective than the listed drug." 21 C.F.R. § 314.127(a)(8). Under the statutory "same labeling" mandate, the principle of a seamless transition to a substituted product, without compromise of safe and effective use, is simply inviolable.

In the context of dosing instructions concerning administration of a drug with or without food, or by sprinkling on food, FDA has established a clear precedent under Hatch-Waxman – requiring a reversal of prior agency policy – that a proposed generic copy can not deviate from the RLD. In 1979, FDA published a proposal to make available to the public a list of approved prescription products with therapeutic equivalence evaluations. 44 Fed. Reg. 2932 (January 12, 1979).[44] In the preamble to that proposal, and thereafter in response to a comment, FDA took the position that "there may occasionally be variations among pharmaceutically equivalent products in the labeling instructions on dose and administration." *See id.* at 2952 and 45 Fed. Reg. 72582, 72599 (October 31, 1980).[45] As an example of such permissible differences, the agency indicated that a particular brand of an antibiotic might require administration on an empty stomach, while another brand might permit administration without regard to food intake on the basis of blood level studies done after administration in the presence of food. In such a case, FDA asserted, "an evaluation of therapeutic equivalence applies only when these products are taken in accordance with labeling directions for the particular products." 45 Fed. Reg. at 72599.

Following enactment of the Hatch-Waxman Amendments with the "same labeling" requirement for generic products, FDA reversed course. Since passage of the Amendments, the Agency has consistently ruled that variations in labeling concerning administration of a drug with or without food, or sprinkled upon food, are not permissible. To assure labeling

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[44] The proposal included a discussion of the rationale for the list, FDA's asserted legal authority, and the criteria FDA would apply in making therapeutic equivalence determinations. The proposal was couched as a proposed amendment to FDA's public information regulations that would announce the availability of such a list. The list, and FDA's criteria for therapeutic equivalence determinations, were forerunners to the *Orange Book*, which the Hatch-Waxman amendments essentially codified (by requiring that FDA publish such a list).

[45] Specifically, FDA described the comment on its proposal as follows: "One comment objected to FDA's position that there may be variations in the labeling instructions for drug administration among pharmaceutically equivalent products and that judgments of therapeutic equivalence can be made only when each product is taken in accordance with its particular labeling directions. The comment argued that because these products are listed as being therapeutically equivalent, they will be considered interchangeable."

conformity, FDA requires ANDA sponsors to conduct food-related bioequivalence studies rather than allowing differences in labeled conditions of use.[46]

b. FDA Has Already Recognized that for Generic Copies of Drug-Device Combinations that Require Patient Training, Differences in Dosing and Handling Instructions are Impermissible and May Not Be Further Investigated in "Actual Use" Studies

As if straightforward statutory interpretation and the regulatory precedents discussed above were not in themselves conclusive, FDA's recent response to two citizen petitions raising questions about generic copies of auto-injectors leaves no doubt that a generic copy of any Inhalation Product cannot deviate from the RLD in instructions for dosing and handling. The petitions, from King Pharmaceuticals, Inc., were addressed first to follow-on auto-injectors in general, and then to auto-injectors containing sumatriptan succinate injection in particular.[47] They requested a number of actions, including confirmation that no generic auto-injector would be approved with instructions for use that deviated from those of the RLD.

In a July 29, 2009, response to the petitions, FDA declared that "for products that require physician training before unsupervised patient use, differences in operation [of the proposed generic product] that require retraining prior to use are not expected to be acceptable in an ANDA." *King Response*, at 10-11. FDA will evaluate whether patients can transition seamlessly to a substituted generic device, *i.e.*, "whether patients can be safely switched to a new product without retraining by a physician or health care professional." *Id.* at 6. In making this assessment, the Agency will consider "whether any difference in materials, design or operating principles introduces a new risk," which could include both those "intrinsic to the new product and risks associated with switching from one product to the other without additional physician intervention or training." *Id.*

The principles FDA articulated for applying the "same labeling" requirement in the context of auto-injectors are a natural extension of the more general statutory interpretation and regulatory precedents discussed above. FDA explained its approach as follows:

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[46] *See* FDA, *Guidance for Industry, Food-Effect Bioavailability and Fed Bioequivalence Studies* (2002), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070241.pdf (conveying FDA's judgment that differences in labeling concerning use with and without food are *not* permitted, and therefore that additional bioequivalence studies (under fed conditions, or as the case may be, with sprinkling on soft food) must be conducted to allow approval). *See also* Letter from Janet Woodcock, Director, CDER, FDA, to Michael Halstead, Warner Chilcott (May 1, 2009), Docket No. 2008-P-0586 (declining to allow food-related carve-outs to the labeling for a generic product that would result in inconsistent directions for dosage and administration of the RLD (Doryx®)) (Exh. 31); and Letter from Janet Woodcock, Director, CDER, FDA, to Diane Mitrione, Wyeth-Ayerst Research (March 1, 1999), Docket No. 97P-0386/CP1 (requiring generic manufacturer to demonstrate bioequivalence when product (Verelan®) is administered via "sprinkle" over apple sauce rather than allowing variation in labeling for dosage and administration) (Exh. 32).

[47] GSK is the sponsor of New Drug Application No. 20-080, covering Imitrex® (sumatriptan succinate) Injection, which is supplied (among other presentations) for use in the auto-injector Imitrex STATdose System®, the would-be RLD for a generic auto-injector containing sumatriptan succinate. GSK filed comments to the King petition docket. Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040.

> Certain 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. For products that require physician training before unsupervised patient use, differences in operation that require retraining prior to use are not expected to be acceptable in an ANDA. FDA will consider other proposed differences in labeling on a case-by-case basis.

Id. at 10.[48]

Investigation of the clinical impact on patients is not, according to the *King Response*, a legally permissible means of curing differences in instructions that raise questions about safe and effective product use under "real world" conditions of generic substitution. Any such studies – for instance, "clinical usability or human factor studies" – are "beyond the scope of studies that can be reviewed and approved in an ANDA." *Id.* at 7. This would include "human factor analysis, actual use studies, and labeling comprehension studies" that the *King Response* identifies as potentially necessary to explore questions about "proper usage by a targeted patient population." *Id.* at 8. Any such studies – seeking to evaluate the ability of untutored patients to successfully handle a substituted device with different instructions for use – would exceed the "limited confirmatory studies" that FDA has indicated are at the outer limits of an ANDA data package. 57 Fed. Reg. at 17957-58 and 54 Fed. Reg. at 28880.

2. A Generic Copy of an Inhalation Product that Deviates in Its Instructions for Use and Handling Would Compromise Public Health and Violate the "Same Labeling" Requirement

Like the auto-injectors at issue in the *King Response*, the Inhalation Products are complex drug-device combinations that are self-administered, after healthcare professional training, according to detailed instructions for correct use. *See* Section II.A.3, *supra* page 8. As it is, without the complication of generic substitution, patient misuse of inhalers is widely reported, and studies confirm the intensified risk of misuse after substitution of a device with different instructions, with no additional training. As the *Regulatory Note* acknowledges, "interactions between the patient and device may play an important role in determining the effective use of DPI products" and "patient related factors (e.g., patient's perceptions of device, willingness to use, and ability to use correctly) are likely to have a considerable impact on the effective use of DPIs." *Regulatory Note*, at 419.[49] Under the circumstances, to meet legal requirements, adhere

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[48] Thus, as FDA concluded, it would not even matter if the proposed generic device were simpler to use than the RLD. What is essential is that the instructions for use of the two products not be different. This is sound policy since ANDAs are intended to be the vehicles for replication, not innovation.

[49] The authors made this point in the context of switching DPIs, but there is no question that the broader principle also applies to other types of inhalers, including MDIs.

to regulatory precedent, and protect the public health, FDA should not approve any proposed generic copy of an Inhalation Product that deviates in instructions for dosing and handling.

a. Given Documented Patient Misuse of Inhalers and Widely Divergent Instructions, FDA Should Carefully Apply the "Same Labeling" Requirement

During the past two decades, numerous studies have shown that both DPIs and MDIs are frequently misused. Researchers have repeatedly emphasized that effective treatment of patients will be substantially compromised if inhalers are not used correctly.[50]

For example, one observational study found that approximately half of all patients who used DPIs made at least one critical error, and that the percentage of critical errors was different for different devices.[51] In another recent study evaluating four different DPIs, investigators reported that nearly a third of all patients used DPIs ineffectively, and that this error rate increased with age, degree of airway obstruction, and lack of prior training by a healthcare professional.[52] Patients were found to have used their DPIs incorrectly in a number of ways, including loading the DPI during inhalation rather than before, not loading the DPI at all, or exhaling into the device instead of inhaling. These observations led the authors to conclude that the risk of usage errors will only increase as the growing number of available DPIs contributes to the "current inhaler maze."[53] As another investigator declared in a 2006 review article, it is "extremely common" for patients to fail to use inhalers effectively, and thereby receive ineffective treatment, because the devices are not intuitive to use.[54]

Numerous studies have also found that MDIs are frequently misused – in fact, the frequency of misuse of MDIs ranges from 14-90%.[55] Most of the studies found that only a relatively small number of patients typically perform all the tasks required for proper use of an MDI. Many patients, including in particular children and the elderly, have difficulty with hand-breath coordination, and fail to actuate the MDI canister immediately after commencing inspiration. Instead, they do so either when finishing inhalation or during exhalation and, as a result, do not receive the amount of drug necessary for effective treatment.[56] Other critical errors

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[50] *See* Mathieu Molimard and Vincent Le Gros, *Impact of Patient-Related Factors on Asthma Control*, 45 J. Asthma 109 (2008) (Exh. 33); Frederico Lavorini, *et al.*, *Effect of Incorrect Use of Dry Powder Inhalers on Management of Patients with Asthma and COPD*, 102 Respiratory Med. 593 (2008) (Exh. 34); and Martina Schulte, *et al.*, *Handling of and Preferences for Available Dry Powder Inhaler Systems by Patients with Asthma and COPD*, 21 J. Aerosol Med. Pulmonary Drug Delivery 321 (2008) (Exh. 35).

[51] *See* M. Molimard, *et al.*, *Assessment of Handling of Inhaler Devices in Real Life: An Observational Study of 3811 Patients in Primary Care*, 16 J. Aerosolized Med. 249 (2003) (Exh. 36).

[52] *See* Siegfried Wieshammer and Jens Dreyhaupt, *Dry Powder Inhalers: Factors Associated with Device Misuse*, 1 RDD Europe 95 (2009) (Exh. 37).

[53] *Id.* at 101.

[54] *See* Mark L. Everard, *Regimen and Device Compliance: Key Factors in Determining Therapeutic Outcomes*, 19 J. Aerosolized Med. 67 (2006) (Exh. 38).

[55] Molimard, *et al.*, *supra* n. 51.

[56] *See* Graham K. Crompton, *Problems Patients Have Using Pressurized Aerosol Inhalers*, 119 Eur. J. Respiratory Disease Supp. 101 (1982) (Exh. 39).

involving mishandling of MDIs include inhalation by nose and accidental misdirection of the spray cloud against the teeth, tongue, or lips.[57]

These findings are significant because the misuse of inhalers has been found to decrease lung deposition of the active ingredient by anywhere from 7% to 20%, and thereby correspondingly to reduce effective treatment of disease.[58] This has been demonstrated both for beta agonists, such as SAL, and for inhaled corticosteroids, such as FP. For example, one study involving a short-acting beta-agonist found that forced expiratory volume decreased by 30% in patients making inhalation errors, when compared to those who properly used their inhaler.[59] Another study involving an inhaled corticosteroid found that inhaler misuse resulted directly in poorer control of asthma.[60] These observations are corroborated by a literature review published in 2000 that evaluated reports involving the use of various types of devices containing inhaled corticosteroids. It also found that poor inhalation technique is a significant factor contributing to the lack of effectiveness of inhaler therapy for asthma.[61]

These numerous reports linking the misuse of inhalers to ineffective treatment of disease reinforce the importance of holding instructions for dosing and handling constant in the context of generic approval and substitution. The need is particularly acute for children and the elderly, who may have an especially difficult time with correct usage of both MDIs and DPIs.[62] For example, when GSK integrated a dose-counter into its MDI products, it conducted, at FDA's request, a patient handling study across a broad patient population including not only adults, but also elderly and pediatric patients. Accordingly, to the extent that FDA considers differences in the design attributes, performance characteristics, and corresponding instructions for use of a proposed generic product, it should evaluate the permissibility of those differences through a lens that considers the higher likelihood of misuse by children and the elderly. As set forth below, this should be the case both for DPIs and MDIs. While GSK acknowledges that the issue of

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[57] *See* Andrea S. Melani, *et al.*, *Inhalation Technique and Variables Associated with Misuse of Conventional Metered-Dose Inhalers and Newer Dry Powder Inhalers in Experienced Adults*, 93 Annals Allergy, Asthma & Immunology 439 (2004) (Exh. 40).

[58] *See* Stephen P. Newman, *et al.*, *Improvement of Drug Delivery with a Breath Actuated Pressurized Aerosol for Patients with Poor Inhaler Technique*, 46 Thorax 712 (1991) (Exh. 41).

[59] *See* S. Lindgren, *et al.*, *Clinical Consequences of Inadequate Inhalation Technique in Asthma Therapy*, 70 Eur. J. Respiratory Disease 93 (1987) (Exh. 42).

[60] *See* V. Giraud and N. Roche, *Misuse of Corticosteroid Metered-Dose Inhaler is Associated with Decreased Asthma Stability*, 19 Eur. Respiratory J. 246 (2002) (Exh. 43).

[61] *See* Mac G. Cochrane, *et al.*, *Inhaled Corticosteroids for Asthma Therapy: Patient Compliance, Devices, and Inhalation Technique*, 117 Chest 542 (2000) (Exh. 44).

[62] For studies documenting this problem in children, *see* Arvid W.A. Kamps, *et al.*, *Poor Inhalation Technique, Even After Inhalation Instructions, in Children with Asthma*, 29 Pediatric Pulmonology 39 (1999) (Exh. 45); Mandeep Walia, *et al.*, *Assessment of Inhalation Technique and Determinants of Incorrect Performance Among Children with Asthma*, 41 Pediatric Pulmonology 1082 (2006) (Exh. 46); and S. Pedersen, *et al.*, *Errors in Inhalation Technique and Efficiency in Inhaler Use in Asthmatic Children*, 41 Allergy 118 (1986) (Exh. 47). For studies involving the elderly, see S.C. Allen and S. Ragab, *Ability to Learn Inhaler Technique in Relation to Cognitive Scores and Tests of Praxis in Old Age*, 78 Postgraduate Med. J. 37 (2002) (Exh. 48); and Stephen C. Allen, *et al.*, *Acquisition and Short-Term Retention of Inhaler Techniques Require Intact Executive Function in Elderly Subjects*, 32 Age and Ageing 299 (2003) (Exh. 49).

same instructions for use and handling may require attention on a case-by-case basis, as FDA noted in the *King Response*, nonetheless a framework of general principles can be established to assure patients a seamless transition to a generic Inhalation Product, as FDA has done for auto-injectors.

i. Different Instructions and Potential for Misuse of Dry Powder Inhalers

DPIs can generally be categorized into three main categories: (1) pre-metered single-dose inhalers, in which each dose is loaded into the device before use; (2) multiple-dose reservoir inhalers, in which a bulk supply of drug is preloaded into the device (device-metered); and (3) pre-metered multiple dose inhalers, where multiple single doses are included within the device.[63]

DPIs within these categories vary widely in operational techniques. In single-dose DPIs, the drug substance is typically formulated in individual gelatin capsules. Each capsule is placed in the inhaler, where it is pierced or opened when the patient primes the device.[64] The patient then inhales the powder from the broken or opened capsule, which must be removed and replaced with the next capsule. Multiple dose reservoir devices contain a bulk supply of drug from which individual doses are released. Generally, for such devices, the patient must hold the inhaler vertically while actuating the device (by, for example, twisting the base) to release a dose of drug into a metering cup.[65] Finally, multiple dose units utilize individually prepared and sealed doses of drug. The DISKUS is an example of this type of inhaler.[66] It houses a coiled strip of 14, 28, or 60 foil-wrapped individual doses. When the patient slides the lever on DISKUS, the dose-containing blister is locked into place and the two layers of foil on that blister are peeled apart, making the dose ready for inhalation. There is no need to remove spent blisters from the device.

If FDA were to permit ANDA approvals of a generic DPI referencing a DPI in a different category, substantial patient confusion, and a breach of the "same labeling requirement," would inevitably result.[67] The *Regulatory Note* acknowledges 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." *Regulatory Note*, at 419. To avoid that problem, the *Regulatory Note* suggests 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 in order to help ensure the effective use of the generic DPI product.

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[63] *See* H. Chrystyn, *The Diskus: A Review of Its Position Among Dry Powder Inhaler Devices*, 61 Int'l J. Clinical Practice 1022 (2007) (Exh. 50).

[64] Examples of single-dose inhalers include the Spinhaler®, Rotahaler®, Handihaler®, Aerolizer®, and Cyclohaler®. *See Regulatory Note*, at 420.

[65] The Clickhaler®, Easyhaler®, Pulvinal®, Turbuhaler®, and Twisthaler® are multiple dose reservoir devices. *See id.*

[66] Other examples of multiple dose units are the Aerohaler® and Diskhaler®. *See id.*

[67] 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* Wieshammer and Dreyhaupt, *supra* n. 52.

A comparison of the instructions for use of ADVAIR DISKUS (a pre-metered, multi-dose device) and PULMICORT FLEXHALER™ (a reservoir device) illustrates the point. To operate the DISKUS, the patient first exposes the mouthpiece by pushing on the thumb-grip until the mouthpiece appears.[68] The user then releases a dose of drug by sliding a lever until it clicks. Next, the user inhales the drug and then covers the mouthpiece by pushing on the thumb-grip to close the device. The operating instructions for the FLEXHALER are significantly different.[69] For that device, the user first exposes the mouthpiece by twisting off the mouthpiece cover. He or she must then prime the device for first use by twisting the base of the inhaler as far as it will go in one direction and then fully back again in the other direction until it stops. Once the device is primed, the patient loads a dose by holding the tubular unit upright and making the same twisting motions (in one direction and then the other). The user then inhales the drug and covers the mouthpiece by placing the cover back on the inhaler and twisting shut.

Even within the same DPI format, however, inhalers differ in their designs and operating principles, and associated instructions for use.[70] For example, the instructions for use of GSK's RELENZA® DISKHALER®, another pre-metered, multi-dose device, differ substantially from the DISKUS instructions and are actually more complicated than the FLEXHALER instructions.[71] For that device, the user pulls on the mouthpiece to extend and extract the medicine tray out of the body of the device. The patient must then place one medicine disk on the tray and push it back into the device. To release a dose, the user lifts a flap on the device straight up, which punctures the medicine disk; the user then puts the flap back down, inhales, and puts the cover back on the device. After three more doses, the user must replace the disk and repeat this entire process.

ii. Different Instructions and Potential for Misuse of Metered Dose Inhalers

The potential for confusion arising from differences in the labeling and instructions exists for MDIs as well. In a draft guidance document, FDA recognized that proper use of an MDI is critical to clinical efficacy, which requires consideration of

> [a]dministration skills and practices, for example, breath holding and its duration, patient inspiratory flow rate, discharging either via closed lips around the mouthpiece or into the open mouth, coordination of aerosol discharge (actuate and breathe) and inhalation by the patient, add-on devices (e.g., spacers, chambers),

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[68] ADVAIR DISKUS labeling, *supra* n. 36.

[69] PULMICORT FLEXHALER FDA-approved labeling (Exh. 51).

[70] The *Regulatory Note* 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." *Regulatory Note*, at 419.

[71] RELENZA DISKHALER FDA-approved labeling (Exh. 52).

> proper priming of the valve and cleaning practices for the actuator, and proper handling and fitting of the actuator to the valve stem.[72]

And, in the context of transitioning to HFA propellants with the phase-out of CFCs, FDA emphasized the critical importance of proper priming and cleaning of an MDI. Specifically, an information sheet that FDA published about the transition stated that

> [c]leaning the inhaler to prevent clogging and properly priming the albuterol HFA inhaler are very important to make sure that the medicine sprays from the inhaler so you can breathe it into your lungs. Each albuterol HFA inhaler comes with directions for washing, drying the mouthpiece (part that goes in your mouth) and priming. *There are some differences between brands of inhalers, so you will need to follow the directions that come with each inhaler* (emphasis added).[73]

A comparison of the priming and cleaning instructions for ADVAIR HFA and for SYMBICORT® Inhalation Aerosol, a comparable two-active-ingredient maintenance treatment for asthma and COPD formulated in an MDI, illustrates the potential for such differences across MDIs. For example, both MDIs require priming before first use, but ADVAIR HFA requires repriming if the product is not used for four weeks, while SYMBICORT must be reprimed after 7 days.[74] The manner in which the devices must be primed also differs. ADVAIR HFA must be shaken for five seconds and then sprayed, and this process repeated four times, before first use. To reprime after a prolonged period without use or after dropping the device, the user must shake for five seconds and spray, and repeat once. The instructions for SYMBICORT are similar in that they require shaking for five seconds before spraying, but the process is only repeated once regardless of when the priming occurs. The cleaning instructions for the two MDIs also diverge. A user of ADVAIR HFA must use a dry cotton swab to clean the opening where the spray is emitted from the canister, and must wipe the inside of the mouthpiece with a tissue dampened with water. A user of SYMBICORT, on the other hand, must wipe the mouthpiece with a dry cloth.

Accordingly, for both DPIs and MDIs, one need only survey the current landscape of marketed products to find concrete examples of differences in instructions for dosing and handling that would be unmanageable – and contrary to legal requirements – in the context of generic substitution.

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[72] *See Draft CMC Guidance*, *supra* n. 41, at 3.

[73] FDA, *Transition from CFC Propelled Albuterol Inhalers to HFA Propelled Albuterol Inhalers: Questions and Answers, available at* www.fda.gov/Drugs/ResourcesForYou/Consumers/QuestionsAnswers/ucm077808.htm#different (last visited Dec. 9, 2009).

[74] SYMBICORT® FDA-approved labeling (Exh. 53).

b. Incorrect Usage in an Unsupervised Transition to a Substituted Inhaler with Different Instructions Is a Documented Risk, and Further Targeted Study Is Not Compatible with the ANDA Review Pathway

Researchers have established that the risk of incorrect inhaler use intensifies in the context of unsupervised substitution of a new device with different instructions. And as noted earlier in Section II.A.3, *supra* page 8, correct use of the Inhalation Products is sufficiently complex and important to require healthcare professional training of patients prior to initial use. Empirical data reinforce the need for patient training. Recently, one study found that the frequency of handling errors is high when patients use a device for the first time and rely solely on the instructions for use.[75] Yet generic substitution is not accompanied by any special instructions or healthcare practitioner intervention of any kind, and patients and their prescribers may not even know it is taking place, let alone approve or prepare for it.

A recently completed two-year retrospective study involving 824 patients suggests a deterioration of clinical outcomes when inhalers are switched.[76] That study reported that when asthma patients had their inhaled corticosteroid device switched without an accompanying consultation or retraining, their asthma deteriorated compared to the control group. The principal factor that contributed to the worsening of asthma may very well have been the difficulty that patients encountered when they were switched to different inhalers. The authors reported that the odds of unsuccessful treatment were almost twice as high among those patients whose inhalers were switched when compared to patients that did not switch.

To be sure, in the foregoing study, the authors did note that training on the device to which patients were switched would help address certain problems and presumably lead to more effective treatment. But, as FDA recognized in the *King Response*, no reliance can be placed on the intervention of a healthcare practitioner in the context of generic substitution. In fact, if an intervention would be necessary to assure correct use, the "same labeling" requirement would, by definition, be breached. And as a practical matter, regrettably, healthcare practitioners have not proved to be a reliable source of training of patients in any event, let alone in the event of generic substitution. Numerous studies show that patients receive little, if any, training from healthcare professionals on how to use inhalers.[77]

As FDA concluded in the *King Response,* in the case of self-administered products requiring healthcare professional training, such as the Inhalation Products, "differences in operation that require retraining prior to use [and different patient instructions] are not expected to be acceptable in an ANDA." *King Response*, at 10-11. While further investigation of the

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[75] *See* Schulte, *et al.*, *supra* n. 50.

[76] Mike Thomas, *et al.*, *Inhaled Corticosteroids for Asthma: Impact of Practice Level Device Switching on Asthma Control*, 9 BMC Pulmonary Med. 1 (2009) (Exh. 54). The switches evaluated in this study included DPI to regular MDI, different brands of DPI, DPI to breath-actuated inhaler (DPI or MDI), breath-actuated inhaler to regular MDI, and different brands of breath-actuated inhaler.

[77] *See, e.g.*, Michael Smith, *CHEST: Inhalers Difficult Challenge for Asthma, COPD Patients*, MedPage Today, Oct. 24, 2007 (Exh. 55); Lavorini, *et al.*, *supra* n. 50; and Wieshammer and Dreyhaupt, *supra* n. 52.

clinical impacts of such differences could be informative, it lies beyond the scope of an ANDA. *Id.* at 7.

C. A Proposed Generic Copy of an Inhalation Product Cannot Be Approved Unless It Meets Certain Critical Elements of the Emerging Framework for Determining Bioequivalence

1. The Legal Requirement of Bioequivalence for ANDA Approval

The legal framework for bioequivalence determinations is familiar. Under the FDCA, a generic drug is considered bioequivalent to the listed drug 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). If the drug is not intended to be 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 proposed generic drug and the RLD in safety and therapeutic effect. 21 U.S.C. § 355(j)(8)(C). FDA's regulations establish a hierarchy of approaches establishing bioequivalence, and different methods may be combined. 21 C.F.R. § 320.24(a). The choice of study design is, ultimately, "based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug."[78] In order to make a bioequivalence determination using any type of study design, however, 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). Furthermore, the agency should "cogently explain" any decision it does reach; it may not simply issue a "conclusory response." *A.L. Pharma, Inc. v. Shalala*, 62 F.3d 1484, 1492 (D.C. Cir. 1995); *see also Alpharma v. Leavitt, et al.*, 460 F.3d 1 (D.C. Cir. 2006).

Finally, it should be emphasized that where, as here, the RLD has been approved for more than one indication, FDA should confirm the bioequivalence of the generic product to the RLD for each indication in the labeling for the RLD. To be sure, and as mentioned previously, FDA has promulgated regulations allowing a generic manufacturer to "carve out" indications from its proposed labeling. 21 C.F.R. § 314.127(a)(7). But those regulations authorize a labeling "carve out" only if the labeling to be omitted is protected by patent or by exclusivity and the differences will not render the generic drug less safe or effective than the RLD for all remaining, non-protected conditions of use. *See also* 21 C.F.R. § 314.94(a)(8)(iv) (allowing an ANDA applicant to omit from its labeling any "aspect of labeling protected by patent" as long as such changes do not render the generic product less safe and effective than the RLD). A

[78] *See* Letter from Janet Woodcock, CDER, FDA, to Alan Bennett, Ropes & Gray (Nov. 18, 2008), Docket No. FDA-2006-P-0073 (granting in part and denying in part citizen petition of AstraZeneca LP concerning bioequivalence of generic budesonide inhalation products) (Exh. 56).

"labeling carve out" based on a generic sponsor's lack of data necessary to demonstrate bioequivalence in all approved indications is not a permissible basis for omitting an indication. *See id.* In the case of the Inhalation Products, no exclusivity or patent would justify a "carve out."

2. FDA Has Not Articulated Standards Governing Bioequivalence Determinations for Orally Inhaled Products, and the Bioequivalence Framework Is Still in Development

As FDA scientists recently declared in their *Regulatory Note*, demonstrating bioequivalence for orally inhaled products for local action "is more challenging" than for drugs that act by systemic circulation and whose comparative bioavailability can be evaluated by measuring "drug concentration in a relevant biologic fluid (e.g., plasma or blood)." *Regulatory Note*, at 414. Reflecting the complexity, FDA has moved to sponsor research and actively participate in public workshops drawing upon government, industry, and academic expertise to help solidify the science base upon which appropriate bioequivalence standards can be built.[79] Yet the work remains foundational.

Indeed, FDA to date has not issued any guidance to industry (even in draft form) setting forth specific standards and tests for assessing the bioequivalence of orally inhaled drug products. This would entail not only settling upon the parameters to be measured, but also choosing and validating the statistical methodology for comparing those parameters from test and reference products. Take, for instance, aerodynamic particle size distribution ("APSD"), which was originally developed for reasons unrelated to prescription drugs. The pharmaceutical industry adopted the test, but only as a quality control method for assessing batch to batch variability for the same drug product – not as a tool for assessing bioequivalence. While APSD is likely to be a key *in vitro* characteristic in bioequivalence comparisons, there is currently no accepted statistical method for making a comparison of one product's APSD to that of another product. This is due, in part, to the fact that an APSD profile involves multiple variables that are correlated with each other.[80] Multivariate metrics such as APSD lose critical information when represented by a single number that could be directly compared between test and reference products. Efforts by FDA to create a statistical test to capture the particulars of the entire APSD profile and allow for a meaningful comparison have been unsuccessful.

For example, FDA first proposed the chi-square ratio comparison test, publishing it in a 1999 draft guidance document concerning bioequivalence of nasal sprays and nasal aerosols. Several difficulties with the test were brought to light by the Product Quality Research Institute ("PQRI") APSD Profile Comparisons Working Group, including the fact that in some cases, the test could declare two slightly different profiles "more equivalent" than two identical profiles and that laboratories with higher overall variability of measurements would have an easier time

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[79] *See PQRI Meeting, supra* n. 8.

[80] Namely, active pharmaceutical ingredient amounts, both the mean and the variance, in each of the size categories that correspond to specific stages of the Andersen cascade impactor ("ACI"), as well as the way the ACI test is performed.

demonstrating bioequivalence than a laboratory with more precise measurements.[81] FDA then indicated that it might supplement the chi-square ratio test with another test, the impactor-sized mass population test. PQRI found, however, that neither test, nor their combination, produced consistent results.[82] In sum, it is clear that statistical methods and criteria for determining *in vitro* equivalence of orally inhaled products have yet to be established.

However, as noted in the introduction, formative scientific and regulatory deliberations are taking place, and an emerging bioequivalence framework, comprising multiple components of *in vitro* and *in vivo* testing, and addressing sameness of formulation and device components and functioning, can be discerned. In the *Regulatory Note* (which was addressed to DPIs in particular, but has broader application to MDIs, as well), FDA scientists recited "current thinking ... based on the aggregate weight of evidence." This approach entails

> appropriate *in vitro* studies to determine comparative *in vitro* performance of test and reference ... products, pharmacokinetic (or pharmacodynamic) studies to establish equivalence of systemic exposure, and pharmacodynamic (or clinical endpoint) studies to demonstrate equivalence in local action. Formulation and device similarities are also taken into account in ensuring equivalence of these orally inhaled drug products.

Regulatory Note, at 414-415.[83]

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[81] *See* PQRI Profile Comparisons Working Group, Minutes of Teleconference on February 16, 2005, *available at* http://www.pqri.org/commworking/minutes/pdfs/dptc/psdpcwg/021605min.pdf (descriptions of the scenarios referenced in the minutes can be located in the minutes of the earlier teleconferences, such as the September 22, 2004 teleconference, *available at* http://www.pqri.org/commworking/minutes/pdfs/dptc/psdpcwg/092204min.pdf and the October 27, 2004 teleconference, *available at* http://www.pqri.org/commworking/minutes/pdfs/dptc/psdpcwg/070704min.pdf) (Exh. 57).

[82] *See* Wallace P. Adams, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols, Part 1: Background for a Statistical Method*, 8 AAPS PharmSciTech E1 (2007) (Exh. 58) *available at* http://www.aapspharmscitech.org/articles/pt0801/pt0801004/pt0801004.pdf; David Christopher, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 2 - Evaluation of a Method for Determining Equivalence*, 8 AAPS PharmSciTech E1 (2007) (Exh. 59), *available at* http://www.aapspharmscitech.org/view.asp?art=pt0801005; David Christopher, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 3 – Final Report on a Statistical Procedure for Determining Equivalence*, 8 AAPS PharmSciTech E1 (2007) (Exh. 60), *available at* http://www.springerlink.com/content/l02816x253720413/fulltext.pdf.

[83] By no means does this Petition address every necessary element of adequate bioequivalence standards for orally inhaled products. The "current thinking" recited in the *Note* reflects what appears to be an emerging consensus about a bioequivalence framework comprising multiple components of *in vitro* and *in vivo* testing, and addressing sameness of formulation and device components and functioning. In a great many indispensable respects, *e.g.*, the need for comparative testing of APSD, as necessary across a range of flow rates reflective of the different inspiratory capabilities of prospective users of a generic inhaler, there appears to be general agreement, thus obviating any need for special attention in this Petition. Even in areas of apparent convergence, such as the need for comparative APSD testing, GSK notes that much remains unresolved, such as the choice (and *a priori* specification) of statistical methods and acceptance criteria.

Prevailing expectations are that the formulation of a proposed generic copy would be qualitatively ("Q1") and quantitatively ("Q2") the same as the RLD formulation ("Q1/Q2 sameness"). The *Regulatory Note* states that

> It is generally suggested that the formulation of the test product be Q1 and Q2 the same as the reference product. Q1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product. Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product. This formulation equivalence recommendation is generally expected to increase the likelihood of establishing bioequivalence of the test and reference DPI products, particularly when the same or similar DPI devices are used. However, this recommendation alone is not sufficient to ensure bioequivalence.

Id. at 419. FDA took the same position in the context of articulating (draft) standards for establishing the bioequivalence of nasal sprays and aerosols,[84] and in disposing of a citizen petition concerning generic budesonide inhalation products.[85] However, the *Regulatory Note*, and FDA's 2007 document, *Critical Path Opportunities for Generic Drugs,*[86] have raised a question of whether Q1 and Q2 differences for inhalation products might be supportable scientifically.[87]

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[84] *See* FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* 8 (2003), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070111.pdf (hereafter the "*Nasal Spray Guidance*") (FDA recommends that the formulation of a proposed generic product be qualitatively ("Q1") the same and quantitatively "essentially the same" ("Q2") as the reference formulation, with "essentially the same" meaning that the concentration/amount of any ingredient(s) in the test product not differ by more than 5% from the concentration/amount in the reference product). *See also* Wallace P. Adams, *The June 1999 Draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays: History, Recommendations and Local Delivery Issues,* Presented at OINDP Subcommittee of Advisory Committee for Pharmaceutical Science, July 2001, *available at* http://www.fda.gov/ohrms/dockets/ac/01/slides/3763s1_04_adams.ppt (recommending that formulation equivalence means Q1 of identical active/inactive ingredients and Q2 of inactive ingredients within ±5% of reference) (Exh. 61).

[85] *See* Letter to Alan Bennett, *supra* n. 78 (finding that requirement of Q1/Q2 sameness would – with inactive ingredients being completely dissolved – allow for unimpeded measurement and comparison of suspended drug particles in the test and reference formulations, thereby potentially obviating the need for clinical studies).

[86] FDA, Critical Path Opportunities for Generic Drugs (May 1, 2007), *available at* www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/CriticalPathOpportunitiesReports/ucm077250.htm#inhalation (hereafter the "*Critical Path Document*").

[87] The *Regulatory Note* suggests that a variation from Q2 sameness may be necessary since the internal design of a proposed generic DPI (*e.g.*, the dimension and shape of channels) may differ from that of the RLD in order to work around the innovator's intellectual property. The *Note* posits that since formulation and device characteristics work in tandem to influence *in vitro* DPI performance, the drug-to-excipient ratio in the test formulation might be adjusted, in light of device modifications, to achieve equivalence.

3. The Formulation of a Proposed Generic Copy of an Inhalation Product Should Be Qualitatively and Quantitatively the Same

Scientific understanding about the performance impacts of formulation differences is too limited to permit any relaxation of the prevailing Q1/Q2 formulation sameness standard, given the need discussed at the outset of this Petition to make bioequivalence determinations vis-à-vis the Inhalation Products with complete confidence. The possibility of a departure from prevailing norms has been raised strictly in an exploratory mode, given the immature state of current knowledge. The *Critical Path Document* reflects the uncertainty:

> In the past, FDA has requested applicants of ANDAs for nasal and inhalation products to formulate products that are qualitatively (Q1) and quantitatively (Q2) the same as the reference product. The acceptability of Q1 and Q2 differences for inhalation products should be explored. Scientific issues involved include 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.

As an initial step toward answering the question on a data-driven basis, at least insofar as DPIs are concerned, the agency recently announced a Request for Proposal (the "RFP") for a scientific project entitled "Evaluating the Effects of Formulation and Device Changes on In-vitro Performance for Dry Powder Inhalers (DPIs)."[88] But as the RFP implicitly acknowledges by its very existence, the science remains too undeveloped to allow a relaxation of prevailing standards.[89] Work, as FDA has commissioned, is needed "to systematically evaluate the extent

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[88] *See* FDA, Solicitation Number: PRE-09-223-01-00153 ("Evaluating the Effects of Formulation and Device Changes on In-vitro Performance for Dry Powder Inhalers (DPIs)" – Solicitation 2) (posted August 28, 2009), *available at* https://www.fbo.gov/index?&s=opportunity&mode=form&id=4c7edba87c50af0838d8d76b9319e3a2&tab=core&tabmode=list.

[89] As FDA has noted, maintaining prevailing standards for formulation sameness, consistent with the current science base, has implications for potential generic entry to the extent that innovators hold patents claiming formulation aspects of marketed listed drugs. *See id.* at 3 ("In coming years, patents will expire on innovator DPIs. Thus, there is an urgent need for establishing science-based requirements for approval of safe and effective generic DPIs.") GSK acknowledges this interplay. By way of example and not limitation, the following U.S. patents claim formulation aspects of MDIs (formulated with propellant HFA 134a) that are among the Inhalation Products at issue in this Petition: No. 6,251,368 (expiring December 4, 2012), No. 5,658,549 (expiring August 19, 2014); 5,674,472 (expiring October 7, 2014); and 6,743,413 (expiring June 1, 2021). While the Hatch-Waxman Amendments to the FDCA in 1984 created an abbreviated approval scheme for generic drug products, they did not override the fundamental drug regulatory purpose of the FDCA to assure the safety and effectiveness of all drug products marketed in the United States. Indeed, that "essential purpose pervades the FDCA." *FDA v. Brown & Williamson Tobacco Corp.*, 529 U.S. 120, 133 (2000). *See 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 generic drugs far outweighs the marginal interest in the availability of generic drug products."). Accordingly, while FDA is authorized to approve generic drugs, the entry of such products into the marketplace is "subsumed by the overriding necessity of ensuring public access to safe commercial drugs." *Schering Corp. v. Food and Drug Admin.*, 51 F.3d

to which changes in formulation and device influence in vitro performance of a test DPI product and lead to equivalent *in vitro* performance of test and reference DPI products ... [by utilizing] DOEs [Design of Experiments]."[90]

In the face of the current uncertainty, FDA should hold to prevailing norms. Any departure would raise questions and detract from confidence in the ability of a generic copy of an Inhalation Product to deliver equivalent clinical outcomes to asthma and COPD patients. For instance, a change in the drug-to-excipient ratio (as posited in the *Regulatory Note*) could modify absorption characteristics of the drug or the (long-term) safety of the modified formulation in the respiratory system. There is abundant evidence in conventional dosage forms that "inactive" ingredients may alter drug absorption.[91] For pulmonary systems, parallel studies have been limited, and there is insufficient knowledge as to the impact varying excipients has on the *in vivo* performance of inhaled formulations. Nonetheless, there are data, including data specifically for MDIs, supporting the notion that at least certain excipients may affect absorption of certain drugs in the respiratory system.[92] These studies suggest that excipients may change the properties of the airway surface liquid (pH, viscosity, etc.), as well as a drug's onset of action, residence time, and *in vivo* dissolution rate. They may also inhibit or promote metabolizing enzymes, epithelial permeability or mucociliary clearance. Thus, equivalent safety and efficacy of products with different drug-to-excipient ratios cannot be assumed.

Change in electrostatic charge, and related alterations in drug deposition patterns under certain conditions of use, is yet another example of how clinical outcomes could vary with formulation differences in ways not susceptible of detection in standard comparative *in vitro* testing. Studies have shown that changes in MDI formulation can have a variety of impacts on product characteristics and performance, including not only stability and fine particle mass, but

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390, 396 (3rd Cir. 1995). Of course, manufacturers seeking approval of follow-on versions of the Inhalation Products may seek FDA approval under Section 505(b)(2) of the FDCA. 21 U.S.C. § 355(b)(2).

[90] RFP, *supra* n. 88, at 7.

[91] *See, e.g.*, D.A. Adkin, *et al.*, *The Effects of Pharmaceutical Excipients on Small Intestinal Transit*, 39 Brit. J. Clinical Pharmacology 381 (1995) (Exh. 62); Bhagwant D. Rege, *et al.*, *Effect of Common Excipients on Caco-2 Transport of Low-Permeability Drugs*, 90 J. Pharmaceutical Sci. 1776 (2001) (Exh. 63); Bhagwant D. Rege, *et al.*, *Effect of Nonionic Surfactants on Membrane Transporters in Caco-2 Cell Monolayers*, 16 Eur. J. Pharmaceutical Sci. 237 (2002) (Exh. 64); Julia D.R. Schulze, *et al.*, *Concentration-Dependent Effects of Polyethylene Glycol 400 on Gastrointestinal Transit and Drug Absorption*, 20 Pharmaceutical Res. 1984 (2003) (Exh. 65); M. L. Chen, *et al.*, *A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol*, 24 Pharmaceutical Res. 73 (2007) (Exh. 66).

[92] *See, e.g.*, Yuko Saso, *et al.*, *Effect of Lecithin Coating on the Pulmonary Absorption of Furosemide in Rats*, 29 Biological Pharmaceutical Bull. 1445 (2006) (Exh. 67); Per Wollmer, *et al.*, *Surface Active Agents as Enhancers of Alveolar Absorption*, 17 Pharmaceutical Res. 8 (2000) (Exh. 68); Keigo Yamada, *Control of Pulmonary Absorption of Drugs by Various Pharmaceutical Excipients*, 127 Yakugaku Zasshi 631 (2007) (Exh. 69); Keigo Yamada, *et al.*, *Carrageenans Can Regulate the Pulmonary Absorption of Antiasthmatic Drugs and Their Retention in the Rat Lung Tissues without Any Membrane Damage*, 293 Int'l J. Pharmaceutics 63 (2005) (Exh. 70); Akira Yamamoto, *et al.*, *Control of Pulmonary Absorption of Water-Soluble Compounds by Various Viscous Vehicles*, 282 Int'l J. Pharmaceutics 141 (2004) (Exh. 71); Lin He, *et al.*, *Improvement of Pulmonary Absorption of Insulin and Other Water-Soluble Compounds by Polyamines in Rats*, 122 J. Controlled Release 94 (2007) (Exh. 72); A.N.O. Dodoo, *et al.*, *Systematic Investigations of the Influence of Molecular Structure on the Transport of Peptides Across Cultured Alveolar Cell Monolayers*, 17 Pharmaceutical Res. 7 (2000) (Exh. 73); and R. C. Boucher, *Chemical Modulation of Airway Epithelial Permeability*, 35 Envtl. Health Persp. 3 (1980) (Exh. 74).

also charge distribution.[93] The interaction between the active ingredient(s) in an inhaler, device components, and excipients (including propellants) can produce a distinctive plume charge.[94] Any differences in charge could alter drug deposition patterns in patients who dose MDIs with a spacer,[95] as an electrostatic interaction between the plume and the spacer can play a role in the final dose received.[96] Yet comparative *in vitro* testing that is expected to be part of the "weight of evidence" bioequivalence package for a prospective generic copy of an Inhalation Product would not detect any differences in electrostatic charge – even if such testing, as the *Regulatory Note* proposes, were done across a range of cascade impactor flow rates.

In sum, understanding of performance impacts (including potentially subtle impacts) of formulation differences on MDIs and DPIs is simply not characterized enough to justify a departure from prevailing Q1/Q2 formulation sameness norms, for purposes of bioequivalence determinations.

4. A Proposed Generic Copy of an Inhalation Product Should Not Be Declared Bioequivalent Unless It Is Successfully Clinically Tested in Each Distinct Indication/Patient Population

Bioequivalence determinations for the Inhalation Products are complicated by their approval for both adults and pediatric patients (depending on the product, as young as 4 or 12 years old), and for both asthma and COPD. As detailed below, due to pathophysiological differences and inhaler handling issues across patient populations and disease states, broad extrapolation of clinical testing results across these separate domains for bioequivalence purposes is not justifiable scientifically.

FDA has refused to allow extrapolation of bioequivalence results from one distinct segment of product use to another if there is reason to believe that drug delivery performance will be inconsistent between the two. For instance, in a recent citizen petition response, FDA agreed with the sponsor of Derma-Smoothe F/S (fluocinolone acetonide 0.01 % topical oil) that separate bioequivalence testing would be required for applications to the body and to the scalp, due to pathophysiological differences in the two regions:

> The vasoconstrictor assay is usually performed on the forearm and it measures vasoconstriction when a topical corticosteroid is

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[93] *See e.g.*, Philippe Rogueda, *Novel Hydrofluoroalkane Suspension Formulations for Respiratory Drug Delivery*, 2 Expert Opinion Drug Delivery 635 (2005) (Exh. 75).

[94] *See Regulatory Note* at 418 ("like the physicochemical properties of a dry powder formulation, the materials used to construct DPIs can affect accumulation of electrostatic charge [footnote omitted]. Some inhaler materials may accumulate and retain electrostatic charge more strongly than others, resulting in a reduced efficiency of drug release from a DPI device and a greater variation in characteristics of delivered aerosols.").

[95] A spacer, or "valved holding chamber," may be used with an MDI by patients, particularly children, who have difficulty coordinating inhalation with actuation of the inhaler. *See, e.g.*, FLOVENT HFA labeling, *supra* n.35. The addition of a spacer can increase the fine particle fraction while decreasing the amount of large particles that lodge in the throat and are subsequently swallowed.

[96] F. Pierart *et al.*, *Washing Plastic Spacers in Household Detergent Reduces Electrostatic Charge and Greatly Improves Delivery*, 13 Eur. Respiratory J. 673 (1999) (Exh. 76)

> applied to the skin. The vasoconstrictor assay has been used to compare topical corticosteroid products that are intended for use on various parts of the body, but it has not been validated as appropriate for use on the scalp. [footnote omitted] As a result, given the potential for terminal hairs to affect the product's ability to reach the skin's surface, FDA agrees that, based on the information before it at this time, there does not appear to be a sufficient scientific basis to conclude that a vasoconstrictor assay conducted on the forearm can appropriately be used as the sole method to establish a generic's bioequivalence to the RLD when both are intended for use on the scalp.[97]

FDA took a similar position in responding to a citizen petition from GSK concerning approval standards for ANDAs for FP nasal spray suspension products. Specifically, the Agency determined that separate clinical testing (for bioequivalence purposes) in different subtypes of rhinitis would have been required had there been "evidence, or reason to believe, that the drug delivery performance will not be the same in ... [a particular subtype of rhinitis] patients and that products will not have equal effectiveness for other indications that have the same site of action."[98] Here, given pathophysiological differences, there is substantial evidence and every reason to believe that drug delivery performance between adult and pediatric patients, and between asthma and COPD, will not be the same.

a. Clinical Testing Is Necessary to Any Determination of Bioequivalence Between Inhalers

The emerging "weight of evidence" approach to assessing bioequivalence of orally inhaled products includes, for good reason, clinical testing to assess safety ("off target" systemic absorption, as measured by pharmacokinetic or pharmacodynamic trials) and efficacy (equivalent local action as a proxy for equivalent availability at the site of action, as measured by pharmacodynamic or clinical endpoint trials).

A consensus seems to have formed around the need to complement comparative *in vitro* testing with clinical trials as part of the assessment of bioequivalence between orally inhaled products.[99] Based on a comprehensive review of the scientific literature evaluating the link between APSD data and the clinical response of inhaled drugs, several investigators cautioned against relying on such *in vitro* information for bioequivalence purposes. They indicated that "attempts to use [cascade impactor] generated data from quality control testing to compare

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[97] *See* Letter from Janet Woodcock, Director, CDER, FDA, to Jerry Roth, Hill Dermaceuticals, Inc., 20 (March 25, 2009), Docket No. FDA-2004-P-0215 (granting in part and denying in part a citizen petition filed by Hill Dermaceuticals concerning prospective generic copies of Derma-Smoothe F/S) (hereafter "*Hill Response*") (Exh. 77).

[98] *See* Letter from Randall W. Lutter, Ph.D., Acting Associate Commissioner for Policy and Planning, FDA, to McGuire Woods LLP, GlaxoSmithKline, and Frommer Lawrence & Haug, LLP, 12 (Feb. 22, 2006), Docket Nos. 2004P-0206/CP1; 2004P-0239/CP1; 2004P-0348/CP1; and 2004P-0523/CP1 (Exh. 78

[99] FDA reached the same conclusion in the context of articulating standards to govern bioequivalence of nasal aerosols and nasal sprays formulated as suspensions. *See Nasal Spray Guidance, supra* n. 84.

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."[100] Other reports in the literature echo the same concerns.[101]

An investigation into alternative DPIs by GSK researchers vividly illustrates the limitations of *in vitro* testing to predict clinical results.[102] When delivered in two different DPIs with the same airflow resistance and polymer composition, a particular dry powder formulation delivered comparable *in vitro* performance and clinical efficacy and safety data. Yet despite those findings, the pharmacokinetic and pharmacodynamic profile of the two devices differed markedly. In particular, systemic exposure to the active drug ingredients was approximately two-fold greater with one device as compared to the other.

b. Separate Clinical Testing for Bioequivalence Purposes Is Necessary for Pediatric Patients, as Extrapolation from Adult Patients Is Not Scientifically Appropriate Due to Pathophysiological Differences and Inhaler Handling Issues

An Advisory Committee meeting last year reviewing the asthma benefit/risk profile of long-acting beta agonists (including SAL) highlighted pathophysiological and developmental differences among adults and children with asthma, particularly young children. As a result of these differences, the "severity of the disease, and the response to therapy, [are] very different in young children compared to older children and adults."[103] At the same meeting, FDA's Director of the Office of Pediatric Therapeutics noted that it is not unusual to find that drug products, which were originally approved for adults, are not as efficacious for children. In fact, she stated, such products may also "have a different safety profile or more severe adverse event profile in children."[104]

In the context of defining approval standards for follow-on inhalers, the European Medicines Agency ("EMEA") has recently recognized these very same concerns. In its guidance for clinical documentation of therapeutic equivalence between two inhaled products for the

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[100] *See* Jolyon Mitchell, *et al.*, *In Vitro and In Vivo Aspects of Cascade Impactor Tests and Inhaler Performance: A Review*, 8 AAPS PharmSciTech 110, E1 (2007) (Exh. 79).

[101] *See* Steve Newman, *Clinical Relevance Of In Vitro Particle Sizing Data,* Presentation at IPAC-RS Nov. 2006 Conference, *available at* http://ipacrs.com/ipac2006.html (Exh. 80); Jolyon P. Mitchell, *What Do Cascade Impaction Measurements Tell Us: In Vitro Aspects*, Presentation at IPAC-RS Nov. 2006 Conference, *available at* http://ipacrs.com/ipac2006.html (Exh. 81); Stephen P. Newman and Hak-Kim Chan, *In Vitro/In Vivo Comparisons in Pulmonary Drug Delivery*, 21 J. Aerosol Med. Pulmonary Drug Delivery 77 (2008) (Exh. 82).

[102] *See* Peter 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 (2009) (Exh. 83).

[103] Statement of Brahm Goldstein, M.D., Industry Representative, Pediatric Advisory Committee, Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee held on December 10-11, 2008, Day 2, at 94, *available at* http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy (Exh. 84).

[104] Statement of M. Dianne Murphy, M.D., Director, Office of Pediatric Therapeutics, *id.* at 17.

treatment of asthma and COPD ("*EMEA Guideline*"), the EMEA declared that "[i]n children, safety data cannot be extrapolated from data generated in adults with asthma or from a surrogate adult population."[105] While the EMEA indicated that data from adult populations can be informative for pediatric patients, it emphasized that there are a number of differences between adults and children (particularly younger children), and between children with asthma and children with normal airway function, which caution against extrapolation. Since "products may be equivalent in adults but may not be equivalent in children," the *EMEA Guideline* declares that "extrapolation from studies in adults, or from studies in adults coupled with *in vitro* data, or the study of a surrogate adult population or the study of normal healthy children, may be unsafe and difficult to justify."[106]

In explaining the requirement of separate studies in pediatrics, the *EMEA Guideline* focused on patient-device interactions of two types that can be expected to vary between adults and pediatric asthmatics, and thus preclude extrapolation of bioequivalence clinical results from one to the other. First, the *EMEA Guideline* highlighted pathophysiological differences:

> The airway in the younger child differs from the airway in the adult and the amount of the dose of an inhaled drug reaching the lower airway in an infant and in a young child will differ from the amount which would reach the lower airway in an adult. The child displays different breathing patterns and has differing tidal volumes, airway geometry, etc. compared with adults. Resistance and inspiratory flow differ between the older child/adolescent and the younger child.[107]

Second, the *EMEA Guideline* highlighted differences in inhalation technique, and the unique challenges younger patients face in handling inhalers:

> The characteristics of the delivery device may be such that the device is more difficult for a child to use than it is for an adult and therefore the child is less able to use the device correctly, or the child may use the device differently from an adult. Such differences in the handling of the product by a child may result in a changed risk/benefit relationship in the child compared with that seen in the adult.[108]

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[105] *See* EMEA, *Guideline On The Requirements For Clinical Documentation For Orally Inhaled Products (OIP) Including The Requirements For Demonstration Of Therapeutic Equivalence Between Two Inhaled Products For Use In The Treatment Of Asthma And Chronic Obstructive Pulmonary Disease (COPD) In Adults And For Use In The Treatment Of Asthma In Children And Adolescents*, at 16 (2009), *available at* http://www.emea.europa.eu/pdfs/human/ewp/415100enfin.pdf (Exh. 85).

[106] *Id.* at 19.

[107] *Id.*

[108] *Id.*

Extensive research demonstrates the unique challenges faced by pediatric patients in using MDI and DPI devices, and the adverse clinical impacts of improper inhaler use.[109] GSK requests that FDA proceed with the same caution as the EMEA. For purposes of bioequivalence, clinical testing results in adults with asthma are simply not adequately predictive of results in children, and should not be extrapolated.

c. Separate Clinical Testing for Bioequivalence Purposes Is Necessary for Chronic Obstructive Pulmonary Disease Patients, as Extrapolation From Asthma Patients Is Not Scientifically Appropriate Due to Pathophysiological Differences and Inhaler Handling Issues

For similar reasons involving differences in patient-device interactions, extrapolation from bioequivalence clinical testing results in asthma to COPD, or vice-versa, is not appropriate. GSK acknowledges that the *EMEA Guideline* supports such extrapolation under defined conditions, particularly where *in vitro* studies demonstrate comparable performance across a range of inspiratory flow rates (pressure drops) that are considered appropriate for all patients for whom the generic product will be used.[110] GSK believes, however, that, the *EMEA Guideline* does not give sufficient weight to the differences in pathophysiology and inhalation technique/capability between asthma and COPD patients.

Asthma and COPD patients differ in more than just inspiratory capability, which testing across a range a flow rates is meant to address. Pathophysiological differences between the two disease states[111] cast serious doubt on whether drug deposition patterns in one are predictive of the other. Specifically, the architecture of the lungs and airways among patients in the two disease states diverge, just as they diverge between patients without lung disease at all and patients in these two groups.

Despite these differences, the EMEA has suggested that if a generic applicant demonstrates that a test and reference product produce similar *in vitro* and *in vivo* results in one disease state (*e.g.*, asthmatics), such results may be extrapolated to another (*e.g.*, patients with COPD) without additional studies. This approach presumes that the comparative performance of a test and reference product in asthmatics will be predictive of that in patients with COPD.

The presumption may not be sound. The difficulty of extrapolating results in asthma to COPD was underscored in a recent publication comparing the pharmacokinetic profiles of different inhalers delivering the same doses of budesonide and formoterol, alone or in

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[109] *See* Section II.B.2.a., *supra* page 15. *See also* Richard C. Ahrens, *The Role of the MDI and DPI in Pediatric Patients: Children are Not Just Miniature Adults,* 50 Respiratory Care 1323 (2005) (Exh. 86); Walia, *et al.*, *supra* n. 62; Kamps, *et al.*, *supra* n. 62; A.W.A. Kamps, *et al.*, *Determinants of Correct Inhalation Technique in Children Attending a Hospital-Based Asthma Clinic*, 91 Acta Paediatrica 159 (2002) (Exh. 87); Pedersen, *et al.*, *supra* n. 62

[110] *EMEA Guideline*, *supra* n. 105, at 10-11 ("If clinical studies are needed and the reference product has an authorised indication which includes both asthma and COPD, therapeutic equivalence studies may only be needed in one of the patient populations in order to obtain a marketing authorisation.").

[111] *See* Section II.A.1, *supra* page 4.

combination with each other.[112] There, the authors conducted several studies evaluating, among other things, the pharmacokinetics of those drugs in adults with asthma and in adults with COPD. The results are quite revealing and, in fact, call into serious question the presumption that comparative drug delivery performance in asthma is predictive of that in COPD, and vice-versa.

Specifically, the results showed that in asthmatics, mean exposure to budesonide was similar regardless of whether the budesonide was administered through a combination budesonide/formoterol MDI (the "reference" device) or through a budesonide-only MDI (the "test" device). The same was true for COPD patients. Thus, as depicted below, drug delivery performance results in the two different disease states were comparable insofar as budesonide was concerned.[113]

Comparable Budesonide Exposure in Asthma and COPD

Reference* PK	=	Test† PK	in asthma patients
Reference* PK	=	Test‡ PK	in COPD patients

* Combination of budesonide and formoterol in single MDI (Symbicort®)
† Budesonide-only MDI (non-marketed formulation)
‡ Budesonide-only MDI (same non-marketed formulation) with formoterol-only DPI (Oxis®)

On the other hand, the results show a strikingly different set of results for formoterol exposure. In asthmatics, after treatment with a combination budesonide/formoterol MDI (the "reference" device), mean exposure to formoterol was 13% lower than after treatment with a formoterol-only DPI (the "test" device). If results in one disease state were predictive of results in the other, one would also expect to see lower formoterol exposure after treatment with the reference device than after treatment with the test device in COPD patients. Yet, for that patient population and as illustrated below, mean exposure after treatment with the reference device was actually 18% higher than after treatment with the test device.

Not Comparable Formoterol Exposure in Asthma and COPD

Reference* PK	<	Test† PK	in asthma patients
Reference* PK	>	Test‡ PK	in COPD patients

* Combination of budesonide and formoterol in single MDI (Symbicort®)
† Formoterol-only DPI (Oxis®)
‡ Formoterol-only DPI (Oxis®) with budesonide-only MDI (non-marketed formulation)

[112] Ann Tronde, *et al.*, *Pharmacokinetics of Budesonide and Formoterol Administered Via 1 Pressured Metered-Dose Inhaler in Patients with Asthma and COPD*, 48 J. Clinical Pharmacology 1300 (2008) (Exh. 88).

[113] Mean exposure was evaluated by the pharmacokinetic parameter "area under the curve," or AUC.

Although the results underscore how MDIs and DPIs can have disparate impacts on the systemic absorption of the same drug, they also illustrate how product performance varies across disease state. The formoterol findings demonstrate that drug delivery performance in asthma is not predictive of COPD, and vice-versa.[114] And the fact that patient handling presumably remained constant between the studies underscores the role that disease state plays on comparative product performance.[115]

FDA should be especially reluctant to extrapolate results from one population to another given patient handling issues among children and the elderly, including specifically, elderly patients with COPD.[116] *See* Section II.C.4.b., *supra* page 29. A positive correlation has been found between incorrect inhaler use and the COPD diagnosis both for MDIs and DPIs,[117] meaning that COPD patients were more likely than other patients to use inhalers incorrectly, even after adjusting for age, sex and educational level.[118] This was confirmed in other studies,[119] which demonstrated that "the error rate [of handling a drug powder inhaler] in patients with severe COPD was disproportionately elevated."[120] Some researchers have suggested that the COPD-specific reduction in cognitive abilities may be one of the possible reasons for these observations.[121] Whatever the causes, these data clearly indicate that concerns relating to proper inhaler use by COPD patients – along with pathophysiological differences between asthma and COPD – warrant separate clinical testing for bioequivalence purposes.

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[114] GSK reviewed its clinical trial database and the published literature to determine whether there are pharmacokinetic data available for either FP or SAL that can inform on the issue of whether comparative drug delivery performance in an asthma population is predictive of a COPD population and vice-versa. Available pharmacokinetic data for SAL in the COPD and asthma patient populations are too limited to permit any meaningful assessment. For FP, however, a body of pharmacokinetic data are available across the two patient populations from 13 studies in GSK's clinical trials database using various formulations: ADVAIR DISKUS (asthma and COPD), ADVAIR HFA (asthma only), FLOVENT DISKUS (asthma and COPD), and FLOVENT HFA (asthma and COPD). These studies were not designed to address the question of whether comparative drug delivery performance in one patient population is predictive of the other, and the pharmacokinetic results across the various studies are too variable – particularly in the asthma population – to allow firm conclusions of any kind to be drawn. To the extent that any conclusions can be drawn from these data, it does appear that COPD patients tended to experience higher exposure to FP than asthma patients at comparable dosing levels.

[115] All study participants received training on proper use of the devices to ensure consistency of patient handling.

[116] *See, e.g.*, W. Janssens, *et al.*, *Inspiratory Flow Rates at Different Levels of Resistance in Elderly COPD Patients*, 31 Eur. Respiratory J. 78 (2008) (Exh. 89); Sheba Jarvis, *et al.*, *Inhaled Therapy in Elderly COPD Patients; Time for Re-Evaluation?*, 36 Age and Ageing 213 (2007) (Exh. 90); and Raid A.M. Al-Showair, *et al.*, *Can All Patients with COPD Use the Correct Inhalation Flow with All Inhalers and Does Training Help?*, 101 Respiratory Med. 2395 (2007) (Exh. 91).

[117] Melani, *et al.*, *supra* n. 57, at 446.

[118] Basher Y. Khassawneh, *et al.*, *Handling of Inhaler Devices in Actual Pulmonary Practice: Metered Dose Inhaler Versus Dry Powder Inhalers*, 53 Respiratory Care 324 (2008) (Exh. 92).

[119] Siegfried Wieshammer and Jens Dreyhaupt. *Dry Powder Inhalers: Which Factors Determine the Frequency of Handling Errors?*, 75 Respiration 18 (2008) (Exh. 93).

[120] Al-Showair, *et al.*, *supra* n. 116.

[121] Wieshammer and Dreyhaupt, *supra* n. 52; M. Orth, *et al.*, *Cognitive Deficits in Patients with Chronic Obstructive Pulmonary Disease*, 60 Pneumologie 593 (2006) (Exh. 94).

III. ENVIRONMENTAL IMPACT

Under 21 C.F.R. §§ 25.30(h) and 25.31(a), this Petition qualifies for a categorical exemption from the requirement to submit an environmental assessment.

IV. ECONOMIC IMPACT

Information regarding economic impact will be submitted upon request by FDA following review of this Petition.

V. CERTIFICATION

The undersigned certifies that, to my best knowledge and belief, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to me which are unfavorable to the Petition.

I certify[122] 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 me 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: over the past two years, many of the developments and publications that are significant to this Petition, and to the elaboration of legal and scientific requirements for approval of orally inhaled drug products, took place, including the *Critical Path Document*, the *FDA AdCom*, the *King Response*, the *Regulatory Note*, the *Hill Response*, the *PQRI Meeting*, and the *RFP*. If I received or expect to receive payments, including cash and

[122] A certification of this kind is required under section 505(q)(1)(H) of the FDCA, for all petitions subject to section 505(q). As of the date of this Petition, GSK is not aware of the filing under Section 505(b)(2) or 505(j) of the FDCA of any ANDA or other follow-on application referencing any Inhalation Product. GSK has not received a paragraph IV certification or seen any indication in the media of the filing of an ANDA or other follow-on application referencing any Inhalation Product. Therefore, to the best of GSK's knowledge, this Petition is not subject to the requirements of Section 505(q). 21 U.S.C. § 355(q). However, consistent with the suggestion in FDA's January 2009 draft guidance document titled "Guidance for Industry, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act (2009)," *available at* www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079353.pdf, GSK is incorporating a certification as a precautionary matter. Please note that by "ANDA or other follow-on application referencing any Inhalation Product," GSK means an application that relies upon an Inhalation Product as the reference listed drug, and that contains the same active ingredient(s), in the same dosage form, at the identical or in analogous strength(s). In a press release dated March 23, 2009, SkyePharma PLC announced the filing of an NDA for a fixed-dose combination in an MDI of fluticasone propionate and formoterol. GSK does not market any product containing the active ingredients fluticasone propionate and formoterol in combination.

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 (however, as a GSK employee, I receive compensation). 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,

Katharine Knobil, M.D.
Global Clinical VP
Respiratory Medicine Development Centre
GlaxoSmithKline

cc: Bruce Manheim, Esq., Ropes & Gray LLP
Joy Liu, Esq., Ropes & Gray LLP

VI. LIST OF EXHIBITS IN ADDENDUM

1 Letter from Janet Woodcock, Director, CDER, FDA, to Thomas Rogers, King Pharmaceuticals, (July 29, 2009), Docket Nos. FDA-2007-P-0128 and FDA-2009-P-0040

2 Sau Lawrence Lee, *et al.*, *In Vitro Considerations to Support Bioequivalence of Locally Acting Drugs in Dry Powder Inhalers for Lung Diseases*, 11 AAPS J. 414 (2009)

3 James G. Dickenson, *Woodcock Cites Generic Skepticism as Priority*, Medical Marketing & Media (Jan. 1, 2009)

4 Peter R. Kowey, *Issues in Bioequivalence and Generic Substitution for Antiarrhythmic Drugs*

5 Caroline Cassels, *AES Calls for Definitive Study to Examine Antiepileptic Drug Substitution*, Medscape Medical News (Dec. 3, 2007)

6 The Endocrine Society, *Position Statement on Bioequivalence of Sodium Levothyroxine* (2008)

7 Letter from Donald M. Poretz, MD, President, Infectious Diseases Society of America, to Dr. Janet Woodcock, Acting Director, CDER, FDA (Nov. 14, 2007)

8 Melinda Beck, *Inexact Copies: How Generics Differ From Brand Names*, Wall Street Journal, Apr. 22, 2008

9 Changning Guo, *et al.*, *Evaluation of Impaction Force of Nasal Sprays and Metered-Dose Inhalers Using the Texture Analyser*, AAPS J., 5-6 (2009) (published online June 3, 2009).

10 PQRI Meeting Objective and Agenda

11 American Lung Association, Epidemiology & Statistics Unit, Research Program Services Division, *Trends in Asthma Morbidity and Mortality* (2009)

12 Melonie Heron, *et al.*, *Deaths: Final Data for 2006*, 57 National Vital Statistics Report 14 (2009)

13 National Asthma Education and Prevention Program, National Institutes of Health, *The NAEPP Expert Panel Report 3 (EPR-3) Summary Report 2007: Guidelines for the Diagnosis and Management of Asthma* (2007)

14 Global Initiative for Asthma, *Global Strategy for Asthma Management and Prevention* (2008)

15 American Lung Association, *Trends in Chronic Bronchitis and Emphysema: Morbidity and Mortality* (2009)

16 David M. Mannino, *et al.*, *Chronic Obstructive Pulmonary Disease Surveillance--United States, 1971-2000*, 47 Respiratory Care 1184 (2002)

17 National Institutes of Health, National Heart, Lung, and Blood Institute, *Morbidity and Mortality: 2007 Chart Book on Cardiovascular, Lung, and Blood Diseases* (2007)

18 Global Initiative for Chronic Obstructive Lung Disease, *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease* (2008)

19 Charles Fletcher and Richard Peto, *The Natural History of Chronic Airflow Obstruction*, 1 Brit. Med. J. 1645 (1977)

20 B.R. Celli and W. MacNee, *Standards for the Diagnosis and Treatment of Patients with COPD: A Summary of the ATS/ERS Position Paper*, 23 Eur. Respiratory J. 932, 933 (2004)

21 Roberto Rodriguez-Roisin, *The Airway Pathophysiology of COPD: Implications for Treatment*, 2 J. COPD 253 (2005)

22 American Thoracic Society and European Respiratory Society, *Standards for the Diagnosis and Management of Patients with COPD* (2004)

23 Martin H. Brutsche, *et al.*, *Pharmacokinetics and Systemic Effects of Inhaled Fluticasone Propionate are Different in Asthmatics and Normal Volunteers*, 356 Lancet 556 (2000)

24 S.D. Singh, *et al.*, *Pharmacokinetics and Systemic Effects of Inhaled Fluticasone Propionate in Chronic Obstructive Pulmonary Disease*, 55 Brit. J. Clinical Pharmacology 375 (2003)

25 SEREVENT DISKUS FDA-approved labeling

26 FLOVENT DISKUS FDA-approved labeling

27 FLOVENT HFA FDA-approved labeling

28 ADVAIR DISKUS FDA-approved labeling

29 ADVAIR HFA FDA-approved labeling

30 Letter from Steven Galson, Acting Director, CDER, FDA, to Susan Rinne, Vice-President, Alza Corporation, *et al.* (Jan. 28, 2005), Docket Nos. 2004P-0506/CP1, 2004P-0472/CP1, 2004P-0540/CP1, and 2004P-0340/CP1

31 Letter from Janet Woodcock, Director, CDER, FDA, to Michael Halstead, Warner Chilcott (May 1, 2009), Docket No. 2008-P-0586

32 Letter from Janet Woodcock, Director, CDER, FDA, to Diane Mitrione, Wyeth-Ayerst Research (March 1, 1999), Docket No. 97P-0386/CP1

33 Mathieu Molimard and Vincent Le Gros, *Impact of Patient-Related Factors on Asthma Control*, 45 J. Asthma 109 (2008)

34 Frederico Lavorini, *et al.*, *Effect of Incorrect Use of Dry Powder Inhalers on Management of Patients with Asthma and COPD*, 102 Respiratory Med. 593 (2008)

35 Martina Schulte, *et al.*, *Handling of and Preferences for Available Dry Powder Inhaler Systems by Patients with Asthma and COPD*, 21 J. Aerosol Med. Pulmonary Drug Delivery 321 (2008)

36 Mathieu Molimard, *et al.*, *Assessment of Handling of Inhaler Devices in Real Life: An Observational Study of 3811 Patients in Primary Care*, 16 J. Aerosolized Med. 249 (2003)

37 Siegfried Wieshammer and Jens Dreyhaupt, *Dry Powder Inhalers: Factors Associated with Device Misuse*, 1 RDD Europe 95 (2009)

38 Mark L. Everard, *Regimen and Device Compliance: Key Factors in Determining Therapeutic Outcomes*, 19 J. Aerosolized Med. 67 (2006)

39 Graham K. Crompton, *Problems Patients Have Using Pressurized Aerosol Inhalers*, 119 Eur. J. Respiratory Disease Supp. 101 (1982)

40 Andrea S. Melani, *et al.*, *Inhalation Technique and Variables Associated with Misuse of Conventional Metered-Dose Inhalers and Newer Dry Powder Inhalers in Experienced Adults*, 93 Annals Allergy, Asthma & Immunology 439 (2004)

41 Stephen P. Newman, *et al.*, *Improvement of Drug Delivery with a Breath Actuated Pressurized Aerosol for Patients with Poor Inhaler Technique*, 46 Thorax 712 (1991)

42 S. Lindgren, *et al.*, *Clinical Consequences of Inadequate Inhalation Technique in Asthma Therapy*, 70 Eur. J. Respiratory Disease 93 (1987)

43 V. Giraud and N. Roche, *Misuse of Corticosteroid Metered-Dose Inhaler is Associated with Decreased Asthma Stability*, 19 Eur. Respiratory J. 246 (2002)

44 Mac G. Cochrane, *et al.*, *Inhaled Corticosteroids for Asthma Therapy: Patient Compliance, Devices, and Inhalation Technique*, 117 Chest 542 (2000)

45 Arvid W.A. Kamps, *et al.*, *Poor Inhalation Technique, Even After Inhalation Instructions, in Children with Asthma*, 29 Pediatric Pulmonology 39 (1999)

46 Mandeep Walia, *et al.*, *Assessment of Inhalation Technique and Determinants of Incorrect Performance Among Children with Asthma*, 41 Pediatric Pulmonology 1082 (2006)

47 S. Pedersen, *et al.*, *Errors in Inhalation Technique and Efficiency in Inhaler Use in Asthmatic Children*, 41 Allergy 118 (1986)

48 S.C. Allen and S. Ragab, *Ability to Learn Inhaler Technique in Relation to Cognitive Scores and Tests of Praxis in Old Age*, 78 Postgraduate Med. J. 37 (2002)

49 Stephen C. Allen, *et al.*, *Acquisition and Short-Term Retention of Inhaler Techniques Require Intact Executive Function in Elderly Subjects*, 32 Age and Ageing 299 (2003)

50 H. Chrystyn, *The Diskus: A Review of Its Position Among Dry Powder Inhaler Devices*, 61 Int'l J. Clinical Practice 1022 (2007)

51 PULMICORT FLEXHALER FDA-approved labeling

52 RELENZA DISKHALER FDA-approved labeling

53 SYMBICORT FDA-approved labeling

54 Mike Thomas, *et al.*, *Inhaled Corticosteroids for Asthma: Impact of Practice Level Device Switching on Asthma Control*, 9 BMC Pulmonary Med. 1 (2009)

55 Michael Smith, *CHEST: Inhalers Difficult Challenge for Asthma, COPD Patients*, MedPage Today, Oct. 24, 2007

56 Letter from Janet Woodcock, CDER, FDA, to Alan Bennett, Ropes & Gray (Nov. 18, 2008), Docket No. FDA-2006-P-0073

57 PQRI Profile Comparisons Working Group, Minutes of Teleconference on February 16, 2005

58 Wallace P. Adams, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols, Part 1: Background for a Statistical Method*, 8 AAPS PharmSciTech E1 (2007)

59 David Christopher, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 2 - Evaluation of a Method for Determining Equivalence*, 8 AAPS PharmSciTech E1 (2007)

60 David Christopher, *et al.*, *Product Quality Research Institute Evaluation of Cascade Impactor Profiles of Pharmaceutical Aerosols: Part 3 – Final Report on a Statistical Procedure for Determining Equivalence*, 8 AAPS PharmSciTech E1 (2007)

61 Wallace P. Adams, *The June 1999 Draft BA/BE Guidance for Nasal Aerosols and Nasal Sprays: History, Recommendations and Local Delivery Issues*, Presented at OINDP Subcommittee of Advisory Committee for Pharmaceutical Science, July 2001

62 D.A. Adkin, *et al.*, *The Effects of Pharmaceutical Excipients on Small Intestinal Transit*, 39 Brit. J. Clinical Pharmacology 381 (1995)

63 Bhagwant D. Rege, *et al.*, *Effect of Common Excipients on Caco-2 Transport of Low-Permeability Drugs*, 90 J. Pharmaceutical Sci. 1776 (2001)

64 Bhagwant D. Rege, *et al.*, *Effect of Nonionic Surfactants on Membrane Transporters in Caco-2 Cell Monolayers*, 16 Eur. J. Pharmaceutical Sci. 237 (2002)

65 Julia D.R. Schulze, *et al.*, *Concentration-Dependent Effects of Polyethylene Glycol 400 on Gastrointestinal Transit and Drug Absorption*, 20 Pharmaceutical Res. 1984 (2003)

66 M. L. Chen, *et al.*, *A Modern View of Excipient Effects on Bioequivalence: Case Study of Sorbitol*, 24 Pharmaceutical Res. 73 (2007).

67 Yuko Saso, *et al.*, *Effect of Lecithin Coating on the Pulmonary Absorption of Furosemide in Rats*, 29 Biological Pharmaceutical Bull. 1445 (2006)

68 Per Wollmer, *et al.*, *Surface Active Agents as Enhancers of Alveolar Absorption*, 17 Pharmaceutical Res. 8 (2000)

69 Keigo Yamada, *Control of Pulmonary Absorption of Drugs by Various Pharmaceutical Excipients*, 127 Yakugaku Zasshi 631 (2007)

70 Keigo Yamada, *et al.*, *Carrageenans Can Regulate the Pulmonary Absorption of Antiasthmatic Drugs and Their Retention in the Rat Lung Tissues without Any Membrane Damage*, 293 Int'l J. Pharmaceutics 63 (2005)

71 Akira Yamamoto, *et al.*, *Control of Pulmonary Absorption of Water-Soluble Compounds by Various Viscous Vehicles*, 282 Int'l J. Pharmaceutics 141 (2004)

72 Lin He, *et al.*, *Improvement of Pulmonary Absorption of Insulin and Other Water-Soluble Compounds by Polyamines in Rats*, 122 J. Controlled Release 94 (2007)

73 A.N.O. Dodoo, *et al.*, *Systematic Investigations of the Influence of Molecular Structure on the Transport of Peptides Across Cultured Alveolar Cell Monolayers*, 17 Pharmaceutical Res. 7 (2000)

74 R. C. Boucher, *Chemical Modulation of Airway Epithelial Permeability*, 35 Envtl. Health Persp. 3 (1980)

75 Philippe Rogueda, *Novel Hydrofluoroalkane Suspension Formulations for Respiratory Drug Delivery*, 2 Expert Opinion Drug Delivery 635 (2005)

76 F. Pierart *et al.*, *Washing Plastic Spacers in Household Detergent Reduces Electrostatic Charge and Greatly Improves Delivery*, 13 Eur. Respiratory J. 673 (1999)

77 Letter from Janet Woodcock, Director, CDER, FDA, to Jerry Roth, Hill Dermaceuticals, Inc. (March 25, 2009), Docket No. FDA-2004-P-0215

78 Letter from Randall W. Lutter, Ph.D., Acting Associate Commissioner for Policy and Planning, FDA, to McGuire Woods LLP, GlaxoSmithKline, and Frommer Lawrence & Haug, LLP (Feb. 22, 2006), Docket Nos. 2004P-0206/CP1; 2004P-0239/CP1; 2004P-0348/CP1; and 2004P-0523/CP1

79 Jolyon Mitchell, *et al.*, *In Vitro and In Vivo Aspects of Cascade Impactor Tests and Inhaler Performance: A Review*, 8 AAPS PharmSciTech 110, E1 (2007)

80 Steve Newman, *Clinical Relevance Of In Vitro Particle Sizing Data,* Presentation at IPAC-RS Nov. 2006 Conference

81 Jolyon P. Mitchell, *What Do Cascade Impaction Measurements Tell Us: In Vitro Aspects*, Presentation at IPAC-RS Nov. 2006 Conference

82 Stephen P. Newman and Hak-Kim Chan, *In vitro/In Vivo Comparisons in Pulmonary Drug Delivery*, 21 J. Aerosol Med. Pulmonary Drug Delivery 77 (2008)

83 Peter 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 (2009)

84 Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee and Pediatric Advisory Committee held on December 10-11, 2008, Day 2.

85 EMEA, *Guideline On The Requirements For Clinical Documentation For Orally Inhaled Products (OIP) Including The Requirements For Demonstration Of Therapeutic Equivalence Between Two Inhaled Products For Use In The Treatment Of Asthma And Chronic Obstructive Pulmonary Disease (COPD) In Adults And For Use In The Treatment Of Asthma In Children And Adolescents* (2009)

86 Richard C. Ahrens, *The Role of the MDI and DPI in Pediatric Patients: Children are Not Just Miniature Adults,* 50 Respiratory Care 1323 (2005)

87 A.W.A. Kamps, *et al., Determinants of Correct Inhalation Technique in Children Attending a Hospital-Based Asthma Clinic*, 91 Acta Paediatrica 159 (2002)

88 Ann Tronde, *et al., Pharmacokinetics of Budesonide and Formoterol Administered Via 1 Pressured Metered-Dose Inhaler in Patients with Asthma and COPD*, 48 J. Clinical Pharmacology 1300 (2008)

89 W. Janssens, *et al., Inspiratory Flow Rates at Different Levels of Resistance in Elderly COPD Patients*, 31 Eur. Respiratory J. 78 (2008)

90 Sheba Jarvis, *et al., Inhaled Therapy in Elderly COPD Patients; Time for Re-Evaluation?*, 36 Age and Ageing 213 (2007)

91 Raid A.M. Al-Showair, *et al., Can All Patients with COPD Use the Correct Inhalation Flow with All Inhalers and Does Training Help?*, 101 Respiratory Med. 2395 (2007)

92 Basher Y. Khassawneh, *et al., Handling of Inhaler Devices in Actual Pulmonary Practice: Metered Dose Inhaler Versus Dry Powder Inhalers*, 53 Respiratory Care 324 (2008)

93 Siegfried Wieshammer and Jens Dreyhaupt. *Dry Powder Inhalers: Which Factors Determine the Frequency of Handling Errors?*, 75 Respiration 18 (2008)

94 M. Orth, *et al., Cognitive Deficits in Patients with Chronic Obstructive Pulmonary Disease*, 60 Pneumologie 593 (2006)

Tabs/Exhibits 2-6, 8, 9, 14, 16, 18-24, 33-51, 53, 55, 58-60, 63-76,79, 82, 83, 85-94