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

CITIZEN PETITION

The undersigned submits this petition on behalf of AstraZeneca LP (AstraZeneca) under sections 501 and 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR § 10.30 to request that the Commissioner of Food and Drugs refrain from approving any budesonide inhalation suspension product using PULMICORT RESPULES® (budesonide inhalation suspension) as a reference listed drug (hereinafter follow-on BIS) unless that approval is supported by appropriate legal, scientific, and procedural methodologies.

I. ACTIONS REQUESTED

This petition requests that FDA publish a draft guidance on demonstration of bioequivalence for locally acting oral inhalation suspension products and allow a period of public comment on that guidance before approving any follow-on BIS. AstraZeneca recognizes that publishing a guidance document prior to approving a follow-on product is not a legal requirement; however, advance publication of such a guidance would facilitate addressing the complexities of bioequivalence in this area.

Additionally, this petition requests that FDA use certain methodologies and address certain issues in approving any follow-on BIS. Specifically, these include examination of the legal issues surrounding removal of the once-daily dosing language from the PULMICORT RESPULES labeling, use of a clinical trial program similar to the program outlined below to demonstrate bioequivalence for follow-on BIS, assessment of important product quality parameters for follow-on BIS, and examination of the legal issues raised regarding permissible scope of the Abbreviated New Drug Application (ANDA) statute. In considering the permissible scope of the ANDA statute, AstraZeneca also requests that FDA consider whether § 505(b)(2) provides a more appropriate approval route for a follow-on BIS.

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II. STATEMENT OF GROUNDS

A. Background

In September 2005, AstraZeneca received notice that IVAX Pharmaceuticals, Inc. (IVAX) had filed an ANDA to obtain approval to manufacture follow-on BIS. This petition is being filed today because of AstraZeneca's concerns regarding the bioequivalence testing, product quality, and labeling changes that would be implicated during the approval process for any follow-on BIS.

1. Asthma

Asthma is a chronic inflammatory lung disease characterized by recurrent episodes of breathlessness, wheezing, and coughing. Asthma can be life-threatening – over 4000 Americans died from asthma in 2002[1] – and its prevalence in the United States has increased since 1980.[2] As of 2002, approximately 20 million Americans had been diagnosed with asthma; of those, approximately 12 million suffered an acute exacerbation (an asthma attack) in the prior year.[3] Seven million children suffer from asthma,[4] comprising approximately 9% of all American children under 18.[5] Asthma disproportionately affects inner-city poor populations.[6]

Although asthma cannot be cured, it can be controlled. Controlling the symptoms of asthma and preventing asthma attacks are particularly important in a young pediatric population because of children's inability to assess for themselves when their breathing is starting to deteriorate. The most important class of asthma control medications is inhaled corticosteroids. Inhaled corticosteroids suppress airway inflammation, impacting many manifestations of the disease: they control symptoms, reduce asthma exacerbations, and reduce airway hyperresponsiveness, resulting in fewer urgent care visits or hospitalizations and a reduction in asthma mortality.[7] As has been recognized by the National Heart, Lung, and Blood Institute in

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[1] Ctrs. for Disease Control & Prevention, Nat'l Ctr. for Health Stats., *Asthma Prevalence, Health Care Use and Mortality, 2002, available at* http://www.cdc.gov/nchs/data/asthmahealthestat1.pdf.

[2] *Id.*

[3] *Id.*

[4] *Id.*

[5] GlaxoSmithKline, *Children & Asthma in America*, Executive Summary, Overview http://www.asthmainamerica.com/children_index.html (last visited May 22, 2006).

[6] *See, e.g.*, Am. Lung Ass'n, *Urban Air Pollution and Health Inequities: A Workshop Report*, 109 Environ. Health Perspectives 357 (2001), *available at* http://www.ehponline.org/members/2001/suppl-3/pdf/samet.pdf.

[7] Nat'l Asthma Educ. & Prevention Program, Nat'l Heart, Lung, & Blood Institute, *NAEPP Expert Panel Report, Guidelines for the Diagnosis and Management of Asthma – Update on*

its asthma treatment guidelines, inhaled corticosteroids are the preferred therapy for all forms of persistent asthma, including in young children.[8]

2. PULMICORT RESPULES® (budesonide inhalation suspension)

PULMICORT RESPULES is the only inhaled corticosteroid drug product that is approved in the United States for young children from 12 months to 4 years of age.[9] Budesonide is an anti-inflammatory corticosteroid with low systemic bioavailability. The therapeutic effects of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract.[10] PULMICORT RESPULES is administered via a jet nebulizer, thereby extending inhaled corticosteroid therapy to young children who are unable to coordinate their breathing sufficiently for appropriate use of a metered dose inhaler (MDI) or a dry powder inhaler (DPI). AstraZeneca conducted extensive Phase III clinical trials for PULMICORT RESPULES in young pediatric populations specifically to extend the substantial benefits of inhaled corticosteroids seen in older patients using other devices to children through use of a nebulized product.

AstraZeneca submits this petition to FDA today precisely because AstraZeneca believes that asthmatic children who need inhaled corticosteroid therapy should receive a reliable treatment with established efficacy and safety. Accordingly, it is important to ensure that any follow-on version of BIS is, in fact, as safe and effective as PULMICORT RESPULES. To this end, our petition discusses three points.

→ First, we note certain impermissible directions for use inconsistencies that would result if certain safety and efficacy information that is present in the PULMICORT RESPULES label were removed from any follow-on BIS label.

→ Second, as FDA is well aware, standard bioequivalence measures as widely employed for generic medications are not appropriate for orally inhaled, locally acting suspensions. Thus far, there has been no FDA guidance published on the topic of appropriate bioequivalence testing for locally acting oral inhalation suspensions. However, conducting a thorough comparative clinical program is one potential method for demonstrating bioequivalence in this kind of product. In this petition, AstraZeneca sets forth the outline of a clinical program that would reasonably

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Selected Topics 2002, at 17, *available at* http://www.nhlbi.nih.gov/guidelines/asthma/asthmafullrpt.pdf [hereinafter Asthma Treatment Guidelines]; Samy Suissa, Pierre Ernst, Serge Benayoun, Marc Baltzan & Bing Cai, *Low-Dose Inhaled Corticosteroids and the Prevention of Death From Asthma*, 343 New Eng. J. Med. 332, 332-36 (2000).

[8] Nat'l Asthma Educ. & Prevention Program, Nat'l Heart, Lung, & Blood Institute, *Quick Reference: NAEPP Expert Panel Report, Guidelines for the Diagnosis and Management of Asthma - Update on Selected Topics 2002* (reprinted May 2003), *available at* http://www.nhlbi.nih.gov/guidelines/asthma/execsumm.pdf.

[9] PULMICORT RESPULES is indicated for children from 12 months to 8 years of age, but is particularly important for the young pediatric population from 12 months to 4 years.

[10] PULMICORT RESPULES full prescribing information.

demonstrate bioequivalence for any proposed follow-on BIS. In AstraZeneca's scientific judgment, a less extensive clinical program would not address important factors[11] that must be taken into account when evaluating bioequivalence between two different manufacturers' products in this drug category.

→ Third, although product quality is always an important factor in any drug approval, for this specific kind of product, as FDA has noted, product quality has a more profound, direct effect on safety and efficacy than in other types of ANDA approvals, in part "because of the route of administration and the sensitive nature" of the patient population.[12] For example, chemical contamination could contribute to adverse events like bronchospasm, the very event that budesonide inhalation suspension is indicated to prevent. Therefore, important aspects of product quality – such as impurities and degradation products – must be carefully assessed and managed, particularly because of the pediatric indication.

B. Proposed IVAX Label is Legally Impermissible

In a notice letter pursuant to 21 U.S.C. § 355(j)(2)(B) regarding AstraZeneca's patents directed to once-daily dosing of nebulized budesonide, IVAX has informed AstraZeneca that it is proposing to eliminate references to once-daily dosing from the label of its proposed follow-on BIS.[13] The omitted material would necessarily include all of the safety and efficacy data related to once-daily dosing, leaving significant data gaps in the labeled clinical information for the follow-on drug.

In addition to the once-daily dosing and clinical information, however, the PULMICORT RESPULES® (budesonide inhalation suspension) label states, "In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved."[14] Unlike most inhaled corticosteroids, budesonide inhalation suspension is proven effective when used once daily. Although the lowest effective dose will vary from patient to patient, as the PULMICORT RESPULES label clearly states, it has been established by clinical data that, for a significant patient population, the lowest effective dose of budesonide inhalation suspension is 0.25 mg

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[11] These factors are described *infra* pp. 10-13.

[12] *See infra* note 69.

[13] The removal of patent or exclusivity protected information is done under the authority of FDCA § 505(j)(2)(C), stating that the labeling for the new drug must be the same as the labeling for the reference listed drug, "except for changes required . . . because the new drug and the listed drug are produced or distributed by different manufacturers" and 21 CFR § 314.94(a)(8)(iv), stating that "[l]abeling . . . proposed for the drug product must be the same as the labeling approved for the reference listed drug, except for changes required . . . because the drug product and the reference listed drug are produced or distributed by different manufacturers. Such differences . . . may include . . . omission of an indication or other aspect of labeling protected by patent or accorded exclusivity . . . ."

[14] Because of the side effects that may result from systemic steroid exposure, it is always good medical practice and safest for patients to minimize systemic exposure to steroids.

once daily. Thus, including this downward titration statement in the proposed IVAX label would teach once-daily dosing, but none of the safety or effectiveness data that support once-daily dosing would remain in the label. Continued inclusion of the downward titration statement in the IVAX label, after elimination of the supporting clinical data, would be legally improper because a company may not suggest a dosing regimen that is unsupported by data in its label – inclusion of the downward titration statement would be misleading and result in the drug being misbranded.[15] Therefore, because teaching a dosage unsupported by safety and efficacy data in the label would be a violation of the Federal Food, Drug and Cosmetic Act (FDCA), including the downward titration statement in the proposed IVAX label would be impermissible.

However, omitting this downward titration statement would also be impermissible. There are certain notable side effects that are associated with systemic steroid exposure, including suppression of growth velocity in pediatric populations. Therefore, it is a medical best practice to minimize systemic exposure to steroids. Reflecting this best practice, all FDA-approved labels for corticosteroids indicated for asthma control include an instruction to titrate down to the lowest effective dose.[16] Indeed, the NHLBI asthma treatment guidelines themselves instruct that patients should "step down to the least medication necessary to maintain control."[17] An IVAX label that did not include this downward titration statement would omit important safety information and therefore would not contain the adequate information for use that the regulations require be included in prescription drug labeling.[18]

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[15] FDCA § 502(a) ("A drug . . . shall be deemed to be misbranded -- [i]f its labeling is false or misleading in any particular.").

[16] *See, e.g.,* product information for prednisolone sodium phosphate oral solution ("In order to minimize the potential growth effects of corticosteroids, children should be titrated to the lowest effective dose"); product information for prednisone ("After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small increments at appropriate time intervals until the lowest dosage which will maintain an adequate clinical response is reached."); product information for beclomethasone dipropionate HFA ("As with any inhaled corticosteroid, physicians are advised to titrate the dose of QVAR downward over time to the lowest level that maintains proper asthma control. This is particularly important in children since a controlled study has shown that QVAR has the potential to affect growth in children."); product information for flunisolide HFA ("To minimize the systemic effects of orally inhaled corticosteroids, including AEROSPAN Inhalation Aerosol, each patient should be titrated to his/her lowest effective dose."); product information for fluticasone propionate HFA ("After asthma stability has been achieved, it is always desirable to titrate to the lowest effective dosage to reduce the possibility of side effects."); product information for triamcinolone acetonide ("Note: In all patients, it is desirable to titrate to the lowest effective dose once asthma stability has been achieved.").

[17] *Quick Reference: NAEPP Expert Panel Report, supra* note 8, at 4 & 5.

[18] 21 CFR § 201.100(c)(1) and (d) (Prescription drug labeling must include "adequate information for its use, including indications, effects, dosages, routes, methods, and frequency and duration of administration, and any relevant hazards, contraindications, side effects, and precautions under which practitioners licensed by law to administer the drug can use the drug safely and for the purposes for which it is intended.").

Thus, whether it includes or omits the downward titration statement, IVAX's proposed label would be legally impermissible under the FDCA and FDA regulations. Furthermore, either inclusion (without the supporting clinical data) or omission (in violation of the treatment guidelines) of the downward titration statement would, at best, be either misleading or confusing.

C. Bioequivalence in Non-systemic Inhalation Suspensions Used to Treat Asthma

1. ANDA Requirements

ANDAs are filed by manufacturers seeking regulatory approval for generic versions of previously approved branded drugs. To demonstrate that a generic product is safe and effective, ANDA applicants may reference the safety and efficacy data submitted to FDA for approval of a pioneer product. The statutory parameters for filing and approval of an ANDA are set forth in section 505(j)[19] of the FDCA.

To gain FDA approval under the ANDA provisions, the statute requires that a generic drug:

→ Contain the same active ingredient as a listed drug,

→ Have the same conditions of use as a listed drug,

→ Be identical in strength, dosage form, and route of administration to a listed drug,

→ Be bioequivalent to a listed drug,

→ Have the same labeling as a listed drug (except for certain changes required because the drugs are being produced by different manufacturers),

→ Meet the certification and notification provisions for any patent listed for a reference listed drug product.

Because the bioequivalence requirement listed above is statutory,[20] the Secretary must not approve an ANDA if information submitted in the ANDA is insufficient to prove that the proposed generic drug is bioequivalent to the reference listed drug.[21]

Bioequivalence is generally determined by comparing the rate and extent of absorption of the reference listed drug to the rate and extent of absorption of the proposed generic drug.[22] First,

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[19] 21 U.S.C. § 355(j), also known as FDCA § 505(j). Section 505(j) was implemented by the Hatch-Waxman amendments to the FDCA, Title I of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417 (1984).

[20] FDCA § 505(j)(2)(A)(iv).

[21] FDCA § 505(j)(4)(F); 21 CFR § 314.127(a)(6).

[22] Section 505(j)(8)(B) of the Act reads:
A drug shall be considered to be bioequivalent to a listed drug if--
(i) the rate and extent of absorption of the drug do not show a significant difference from the rate and extent of absorption of the listed drug when administered at the same molar dose of the

formulation equivalence must be established: two products must be both qualitatively (Q1) and quantitatively (Q2) the same. After Q1 and Q2 are established, FDA regulations contemplate several types of bioequivalence (BE) testing.[23] Pharmacokinetic (PK) measurements – the most accurate and reproducible of the BE testing methods listed in the regulations – are clearly preferred by FDA. However, this kind of measurement is less useful when the products are not intended to be absorbed into the bloodstream to elicit their therapeutic effect; that is, when the site of action is local, not systemic.[24]

The FDCA notes that for non-systemic products, the FDA "may establish alternative, scientifically valid methods to show bioequivalence if the alternative methods are expected to detect a significant difference between the drug and the listed drug in safety and therapeutic effect."[25] The regulations authorize FDA to use either "appropriately designed comparative clinical trials" or "any other approach deemed adequate" to establish bioequivalence.[26]

Inhaled corticosteroids are one class of non-systemic drugs for which FDA may establish alternative methods to show bioequivalence. FDA has recently, and after significant work, used this authority to propose, in a draft guidance, a method for determining the bioequivalence of corticosteroid nasal sprays for local action. FDA has also approved a generic version of one of these nasal sprays, fluticasone propionate (Flonase®), after more than three years of review of a fluticasone ANDA. Although there are certain similarities between the nasal and pulmonary products, we will discuss later in this petition the myriad ways in which determining BE – and, therefore, ensuring comparable safety and efficacy – for an inhalation suspension for asthma in general and pediatric asthma in particular is far more challenging.

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therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses; or
(ii) the extent of absorption of the drug does not show a significant difference from the extent of absorption 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 and the difference from the listed drug in the rate of absorption of the drug is intentional, is reflected in its proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

[23] 21 CFR § 320.24.

[24] Indeed, FDA regulations describing potential bioequivalence problems speak directly to many of the issues relevant to inhalation suspensions. *See* 21 CFR § 320.33, setting forth the criteria and evidence that the Commissioner shall consider to identify pharmaceutical equivalents that are not or may not be bioequivalent drug products. Many of the items listed under subsections (e) and (f) would apply to a potential generic budesonide inhalation suspension.

[25] FDCA § 505(j)(8)(C).

[26] 21 CFR § 320.24.

2. FDA's Approach to BE for Corticosteroid Nasal Sprays

Both in a draft guidance document[27] and in a response to various citizen petitions on the topic of fluticasone,[28] FDA discussed what it considered an appropriate methodology for establishing bioequivalence for non-systemic corticosteroid nasal sprays. Although these documents apply only to nasal products, and not to pulmonary products, the challenges FDA addressed are illustrative of difficulties that arise when attempting to assess BE in any locally acting suspension formulation.

For locally acting products, "true" bioequivalence – that is, the rate and extent of absorption – is not measured directly. Rather, FDA looks to the measurement of certain bioequivalence surrogates to determine, in the Agency's scientific judgment, whether any significant differences in rate or extent of absorption exist for two products. In the nasal spray context, FDA has recommended that a bioequivalence determination rely on "(1) qualitative and quantitative sameness of formulation of test and reference products, (2) comparability in container and closure systems, and (3) in vitro and in vivo methods that demonstrate equivalent product performance."[29] For "equivalent product performance" (also termed "therapeutic equivalence"[30]) to be established, the two products must have equivalent local delivery of the

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[27] Ctr. for Drug Eval. & Research, FDA, *Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action* (April 2003) (draft), *available at* http://www.fda.gov/cder/guidance/5383DFT.pdf [hereinafter Draft Nasal Guidance]. This is the second draft guidance on this topic; FDA's first draft guidance on this topic, published in 1999, was significantly revised after FDA examined the comments received. In particular, FDA convened a meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science to address certain bioequivalence and bioavailability issues raised in the comments, such as particle size, particle size distribution, and the potential effect these could have on safety and efficacy of generic products. *See* Transcript of the July 17, 2001 Meeting of the Orally Inhaled and Nasal Drug Products Subcommittee of the Advisory Committee for Pharmaceutical Science, *available at* http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3764t1_01.pdf, http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3764t1_02.pdf, and http://www.fda.gov/ohrms/dockets/ac/01/transcripts/3764t1_03.pdf [hereinafter OINDP Transcript].

[28] Letter from Randall W. Lutter, Acting Associate Commissioner for Policy and Planning, FDA, to various petitioners at 4-5 (Feb. 22, 2006) (responding to petitions filed in FDA Dockets 2004P-0206, 2004P-0239, 2004P-0348, and 2004P-0523) [hereinafter FDA Petition Response].

[29] FDA Petition Response at 4; Draft Nasal Guidance at 5. FDA emphasizes that *in vivo* data is not sufficient to establish equivalence in the face of failed *in vitro* data – that is, all *in vitro* bioequivalence measures must meet acceptance criteria.

[30] OINDP Transcript at 18 (In evaluating bioequivalence, sponsors are really "trying to achieve therapeutic equivalence, and it's important to note that [by] therapeutic equivalence, I mean equivalence of both safety and efficacy of these two products.") (comments of Dale Conner, Pharm.D., Division of Bioequivalence, Office of Generic Drugs, CDER, FDA).

active ingredient and equivalent systemic exposure to the active ingredient.[31] The first two of FDA's three elements – sameness of formulation and comparability in containers – are more readily established through *in vitro* testing. Evaluation of "equivalent product performance" requires *in vivo* studies.

As FDA notes, there are complications inherent in demonstrating equivalent local delivery, resulting in FDA's use of "equivalent effectiveness" as a surrogate marker for local delivery.

> Because it is very difficult to evaluate local delivery directly, FDA concludes equivalent local delivery for nasal suspension spray products when two products demonstrate equivalent effectiveness in a comparative in vivo clinical trial of test and reference products and equivalent in vitro performance measures of test spray devices.[32]

The use of "equivalent effectiveness" as a surrogate for local delivery in the bioequivalence schema requires that certain assumptions be made. Most important, because there may be small differences in product performance that a clinical study is not sensitive enough to detect, FDA augments the clinical effectiveness data with demonstration of equivalence in device performance: "Because the clinical studies alone may not be sensitive enough to detect small differences in product performance, FDA relies on demonstrations of equivalence in both the clinical study and device performance."[33]

Assessment of the systemic exposure component of "equivalent product performance" is more readily accomplished. "For fluticasone propionate nasal spray, systemic exposure to the active ingredient has known risks, so FDA also evaluates in vivo pharmacokinetic studies to ensure that there is not a significant difference between test and reference products with respect to systemic exposure."[34]

The Draft Nasal Guidance recommends that a BE study with a clinical endpoint be performed to demonstrate efficacy equivalence (and, therefore, equivalent local delivery) and that a PK study be performed to establish systemic exposure equivalence.[35] None of the studies would be intended to show a dose-response relationship; they are merely conducted to "confirm the lack of important clinical differences between [test] and [reference] suspension formulation [products]."[36]

After the conclusion of the testing program, "products that demonstrate equivalence in all of the in vitro and in vivo equivalence tests requested of ANDA applicants are deemed

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[31] FDA Petition Response at 4.

[32] *Id.*

[33] *Id.*

[34] *Id.*

[35] Draft Nasal Guidance at 25-26.

[36] *Id.* at 22.

equivalent."[37] That is, if the tests demonstrate that two products are physically and chemically the same, and that the two products have the same therapeutic effect, then FDA – using its scientific judgment – will draw the conclusion that there is no "'significant difference' in the rate and extent of absorption of the drug" at the local site of action, and will deem the drugs bioequivalent.[38]

It is very difficult to establish bioequivalence for a locally acting nasal suspension product. The more than three years that FDA spent reviewing the generic fluticasone propionate ANDA are testament to the difficulties inherent in that process. The difficulties and the complexities of establishing bioequivalence only become more pronounced in the context of locally acting inhalation suspensions for asthma in general and pediatric asthma in particular.

3. Factors Complicating Bioequivalence Measurement and Testing in Follow-on BIS Products

There are certain factors that make it more challenging to determine bioequivalence for follow-on BIS products than it was to determine bioequivalence for locally acting corticosteroid nasal sprays.

Indication. Asthma is a life-threatening disease. Rhinitis is not. The possible consequences to patients of error, such as overlooking some small but significant difference between a follow-on BIS and a reference product when making a bioequivalence determination, are far greater in asthma than in rhinitis.

Long-Term Maintenance. All inhaled corticosteroids for asthma are prophylactic medications. Inhaled corticosteroids *slowly* improve lung function, symptoms, and exacerbations over an extended period of time. The full therapeutic effect of inhaled corticosteroid therapy may take weeks or even months to develop; therefore, classic inhaled corticosteroid efficacy trials for regulatory approval have a treatment period lasting at least 12 weeks.[39] Any *in vivo* evaluation of comparative efficacy between a test and reference product should adhere to that standard.

Symptom-Based Assessment. Objective measures of lung function, such as Forced Expiratory Volume (FEV_1) or Peak Expiratory Flow (PEF), are used to diagnose asthma in older children and adults. In contrast, diagnosing asthma in young children is particularly difficult due to young children's inability to coordinate their breathing for lung function testing. Therefore, a young child's asthma diagnosis must be based on parent, caregiver, or physician subjective symptom assessment. It is well established that efficacy in young children, who cannot perform objective measures of lung function, can be measured by reduction and maintenance of asthma

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[37] FDA Petition Response at 5.

[38] *Id.* at 4.

[39] FDA requires trials of at least 12 weeks for inhalation corticosteroid products, among other clinical trial design considerations. *See* Ctr. for Drug Eval. & Research, FDA, *Guidance for Industry: Clinical Development Programs for MDI and DPI Products* (Sept. 1994), *available at* http://www.fda.gov/cder/guidance/old046fn.pdf.

symptom scores.[40] However, the subjective nature and inherent variability of asthma symptom scores – a particular problem where caregivers assess the symptom scores for young children who cannot report their own symptoms – serve to decrease the "accuracy, sensitivity, and reproducibility" of any study designed to meet a bioequivalence endpoint using symptom scores.[41]

Children v. Adults. Lung deposition of nebulized budesonide in children varies significantly from lung deposition of nebulized budesonide in adults; children receive a lower percentage of the labeled dose deposited into the lungs than do adults.[42] Although this disparity has been clinically demonstrated, the differences between adults and children, including the size of the respiratory tract components, inhalation control, lung capacity, and breathing patterns,[43] also support the conclusion that, when administered the same amount of drug, children will receive a lower dose in the lungs than will adults. This difference has implications for both efficacy and systemic exposure. Given the differences above, any *in vivo* evaluation of comparative efficacy between a test and reference product intended for children should be conducted in a pediatric asthma population. A trial conducted in a young pediatric population would require getting sufficient high-quality data to support drug approval in that population, including determining whether a young child suffers from intermittent or persistent asthma (because the only appropriate clinical trial population is a persistent asthma population) and ensuring adherence to the nebulization process.

One important side effect of inhaled corticosteroid treatment for pediatric asthma is the impact that the treatment may have on growth velocity. An FDA draft guidance on the effect of inhaled corticosteroids on growth in children notes that "[s]ponsors of both intranasal and inhaled corticosteroid products that contain the same active moiety may be able to use pharmacokinetic data to bridge the growth findings associated with one formulation to a second formulation."[44] However, because the dose-response curve for growth suppression is non-linear,[45]

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[40] PULMICORT RESPULES full prescribing information.

[41] 21 CFR § 320.24(b)(4). FDA is generally reluctant to use clinical trials to prove BE for similar reasons.

[42] Lone Agertoft, A. Andersen, Eva Weibull & Soren Pedersen, *Systemic availability and pharmacokinetics of nebulised budesonide in preschool children*, 80 Archives Disease Childhood 241 (1999).

[43] *See, e.g.,* Karen G. Schuepp, Juergen Jauernig, Hettje M. Janssens, Harm A.W.M. Tiddens, Daniel A. Straub, Roland Stangl, Manfred Keller & Johannes H. Wildhaber, *In vitro determination of the optimal particle size for nebulized aerosol delivery to infants*, 18 J. Aerosol Med. 225 (2005); C. O'Callaghan, J. White, J. Jackson, P.W. Barry & A. Kantar, *Delivery of nebulized budesonide is affected by nebulizer type and breathing pattern*, 57 J. Pharmacy & Pharmacology 787 (2005); Jean-Christophe Dubus & Jacob Anhoj, *Inhaled steroid delivery from small-volume holding chambers depends on age, holding chamber, and interface in children*, 17 J. Aerosol Med. 225 (2004).

[44] Ctr. for Drug Eval. & Research, FDA, *Guidance for Industry: Evaluation of the Effects of Orally Inhaled and Intranasal Corticosteroids on Growth in Children* (Sept. 2001) (draft), at 2,

small differences in systemic exposure between two budesonide inhalation suspension products could lead to a larger difference in growth velocity suppression. This systemic exposure to a drug may also be related to other effects, as indicated in the FDA draft guidance on growth studies: "An estimate of the growth effect of a drug, while important by itself, should also be considered an important sentinel of unmeasured systemic effects that can therefore provide additional safety information."[46] Because effects on growth are clearly related to systemic exposure, any follow-on BIS **must** be required to meet the well-accepted criteria for pharmacokinetic bioequivalence (mean ratio of test/reference has 90% confidence interval between 80 and 125% for both AUC and Cmax). A product that does not meet these standards should not and cannot be approved as a generic version of PULMICORT RESPULES® (budesonide inhalation suspension).

Suspension Characteristics and Product Quality. Various characteristics inherent to suspensions should be assessed in making a bioequivalence determination for two inhalation suspension formulations, including, among others, particle size and excipients. For example, particle size and particle size distribution become more meaningful in the pulmonary context because particle size has a direct correlation to where in the airway lining the drug is applied and, accordingly, has a direct effect on efficacy.[47] Particle size also has the potential to influence drug availability to systemic circulation, with a correlated impact on safety concerns such as growth velocity suppression and HPA axis suppression.

Careful evaluation of the variation between two suspension formulations from different manufacturers is particularly important given that there is no currently accepted method for correlation of *in vitro* characteristics of either the suspension in the container or the aerosol produced by the nebulizer to *in vivo* performance for inhalation corticosteroids. This lack of development of *in vitro* to *in vivo* correlation methodology for inhalation products indicates that bioequivalence work *in vivo* must be required for this type of product and that approval cannot rely on *in vitro* data alone. Even if such methodology were developed, it would clearly need to assess the effects of *in vitro* changes on both systemic absorption of the drug and local deposition of the drug in the lung.

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available at http://www.fda.gov/cder/guidance/3787dft.pdf [hereinafter Draft Growth Effects Guidance].

[45] Peter T. Daley-Yates & D.H. Richards, *Relationship between systemic corticosteroid exposure and growth velocity: development and validation of a Pharmacokinetic-Pharmacodynamic model*, 26 Clinical Therapeutics 1905 (2004).

[46] Draft Growth Effects Guidance at 1.

[47] *See, e.g.,* G.R. Rhodes, Shashank Rohatagi, M.S. Gillen, F. Deluccia, D.D. Banerji & P. Chaikin, *In vitro and in vivo techniques used in drug development for evaluation of dose delivery of inhaled corticosteroids*, 41 J. Clinical Pharmacology 7 (2001). As was described by Dr. Wallace Adams of the FDA, "Differences in particle size distribution can affect rate and extent of dissolution and rate and extent of reaching the sites of action, whether it be the local sites for efficacy or systemic sites leading to toxicity, and consequently when particle size and particle size distribution cannot be determined, there are issues with regard to efficacy and safety." OINDP Transcript at 43. *See also* Draft Nasal Guidance at 4-5.

In summary, all of these factors complicate any bioequivalence evaluation for a proposed follow-on BIS. These factors must be accounted for in any clinical program designed to demonstrate therapeutic equivalence – efficacy and safety equivalence – between a potential follow-on product and PULMICORT RESPULES.

D. Suggested Methodology for BE Testing of Follow-on Locally Acting Oral Inhalation Suspensions

FDA has examined, and other parties have suggested, novel methods for determining the bioequivalence of inhaled corticosteroids that would be relevant to PULMICORT RESPULES® (budesonide inhalation suspension).[48] However, none of these has been accepted by FDA. Indeed, despite much data collection, FDA has not yet published a draft guidance document regarding standards for bioequivalence testing for inhalation suspension products. In the absence of such a guidance, it would seem that, currently, the only way to demonstrate therapeutic equivalence of two budesonide inhalation suspension products would be to conduct a robust comparative *in vitro* and *in vivo* clinical program to ensure that the therapeutic effect from, and safety of, a proposed generic product is equivalent to that of the branded inhaled corticosteroid.[49] Here, AstraZeneca suggests a clinical program that would establish therapeutic equivalence – and thus contribute to an FDA finding of no significant difference, which in turn supports a conclusion of bioequivalence – between a generic inhaled corticosteroid and a branded inhaled corticosteroid. Indeed, as is discussed later in this document, whether the approval path for a follow-on BIS product is by ANDA or by § 505(b)(2) application, this kind of clinical program must be completed to demonstrate bioequivalence. This program is based on the current state of scientific knowledge and also on the bioequivalence testing requirements that the FDA has communicated to AstraZeneca when changes in formulation and device have been made for AstraZeneca inhaled products.

At a minimum, a program would consist of the following two trials:

→ An adequate, well-controlled 12-week clinical trial between test and reference products to provide reliable estimates for "equivalent effectiveness."

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[48] One example is Richard C. Ahrens, Mary E. Teresi, Seung-Ho Han, David Donnell, Jennifer A. Vanden Burgt & Cheri R. Lux, *Asthma Stability after Oral Prednisone: A Clinical Model for Comparing Inhaled Steroid Potency*, 164 Am. J. Respiratory Critical Care Med. 1138 (2001).

[49] This presumption stems from the regulations authorizing FDA to use either "appropriately designed comparative clinical trials" or "any other approach deemed adequate" to establish BE. 21 CFR § 320.24. Because FDA has not yet "deemed adequate" or "established" an alternative, scientifically valid method to show BE – as is permitted by the FDCA § 505(j)(8)(C) – by publishing a guidance, the most logical presumption is that conducting an "appropriately designed comparative clinical trial" is the best publicly available, currently acceptable BE option for follow-on BIS products.

→ A PK study to assess bioequivalence of systemic exposure, as a surrogate for systemic long-term effects such as adrenal suppression, growth suppression, osteoporosis, etc.

1. Clinical Trial for Efficacy Equivalence

The following study considerations relate specifically to an ANDA application for a generic nebulized budesonide inhalation suspension, using PULMICORT RESPULES as the reference listed drug.

a) Study Design

Certain considerations must be taken into account when designing a clinical trial to demonstrate the efficacy equivalence of the test and reference products.

→ Any efficacy trial must be conducted in a young pediatric population and must include adequate representation across the labeled age ranges.

→ The selected doses must fall within the ascending portion of the dose-response relationship and not in the flat portion. At least two doses of both products should be studied to define the ascending portion of the dose-response relationship. PULMICORT RESPULES must be included as part of this trial, because the safety and efficacy of PULMICORT RESPULES has been firmly established by the results of pivotal trials.[50] Note that it is difficult to establish a dose-response relationship for inhaled corticosteroids in a mild population using standard outcomes, such as FEV_1, as the dose-response relationship plateaus at relatively low doses.[51] However, establishing the dose-response relationship is essential if bioequivalence is to be shown via a comparative clinical trial methodology. If the trials do not show dose separation, an alternate methodology to demonstrate dose separation should be employed.

→ Because there may only be a small separation of doses due to a flat dose-response curve, the treatment arms should be adequately powered.

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[50] James W. Baker, Michael Mellon, Jeffrey Wald, Michael Welch, Mario Cruz-Rivera & Karen Walton-Bowen, *A Multiple-dosing, Placebo-controlled Study of Budesonide Inhalation Suspension Given Once or Twice Daily for Treatment of Persistent Asthma in Young Children and Infants*, 103 Pediatrics 414 (1999); James P. Kemp, David P. Skoner, Stanley J. Szefler, Karen Walton-Bowen, Mario Cruz-Rivera & Joseph A. Smith, *Once-daily budesonide inhalation suspension for the treatment of persistent asthma in infants and young children*, 83 Annals Allergy Asthma & Immunology 231 (1999).

[51] Shaun Holt, Arieta Suder, Mark Weatherall, Soo Cheng, Phillippa Shirtcliffe & Richard Beasley, *Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis*, 323 BMJ 253 (2001); Jean Bousquet, Rami Ben-Joseph, Mark Messonnier, Evo Alemao & A.L. Gould, *A meta-analysis of the dose-response relationship of inhaled corticosteroids in adolescents and adults with mild to moderate persistent asthma*, 24 Clinical Therapeutic 1 (2002).

→ Secondary endpoints indicative of efficacy should also be evaluated, such as use of rescue medications or nighttime awakenings.

→ Selection of a more severe asthma population helps to demonstrate a dose response and to facilitate wide separation of the two doses for both the test and reference products.

→ Asthma diagnosis is difficult in young children and therefore must be based on a reliable history of at least three wheezing episodes and a positive predictive index for asthma, as defined by the NHLBI guidance for the diagnosis and treatment of asthma[52] to ensure that the study population truly has asthma. Pivotal trials for AstraZeneca's product required that all participants meet the NIH definition for asthma.[53]

→ In children under five years old, reproducible lung function measurement is impossible; inhaled corticosteroid efficacy has to be based on caregiver-reported symptom scores.[54] Variability in symptom scores is greater than variability in lung function testing. Therefore, a larger sample size is required to establish acceptable confidence limits for the estimated comparison between products. Furthermore, acceptable limits of non-inferiority have not been established for this variable, a problem if the study is conducted with a non-inferiority sample size calculation.

→ The placebo response in asthma may be considerable; therefore, a placebo group is advisable, with appropriate safety monitoring and with a clearly demonstrated dose response for both the test product and the reference product. A placebo arm is advisable to ensure that the responses are due to active medication and to assist in dose separation. Alternatively, if a placebo is not included, there should be a statistically and clinically significant separation of doses for both products.

→ A run-in period of at least two weeks is necessary to verify adherence with study procedures (*e.g.*, diary card completion) and to ensure that a minimum asthma symptom score is established, so that baseline symptoms have room to improve.

→ As is typically required of asthma studies, the treatment period must be at least 12 weeks to allow the symptom score response to reach its maximal level and to allow a reasonable assessment of short-term safety issues. This is particularly important in small children, in view of the reduced precision in the efficacy assessment resulting from the inability to measure lung function reliably.

→ The clinical studies should include an assessment of the effects on HPA axis function.

→ Appropriate blinding methods should be employed.

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[52] Asthma Treatment Guidelines, *supra* note 7.

[53] Baker et al., *supra* note 50.

[54] *Id.*; Kemp et al., *supra* note 50.

→ A subset of participants should have serial PK samples drawn under steady-state conditions in all treatment arms in order to assess systemic exposure in the target population.

Having taken all of these points into consideration, AstraZeneca would recommend a five arm randomized multicenter double-blinded parallel group design with a two week run-in period and a 12 week treatment period. Study visits should be required every four weeks. The study would include male and female patients one to eight years old with a greater than six month history of asthma as defined by the NHLBI[55] and with moderate to severe disease, based on prior need for controller therapy and exacerbation history. Subjects with other significant respiratory or general medical diseases, including prematurity, would be excluded.

A subject would be randomized to one of the five treatment arms, with treatment administered via nebulizer. The required treatment arms, taking into consideration the points mentioned above, would be:

→ Follow-on BIS product low dose

→ Follow-on BIS product high dose

→ PULMICORT RESPULES low dose

→ PULMICORT RESPULES high dose

→ Placebo

All subjects previously taking inhaled corticosteroids would be required to discontinue these drugs at randomization for the remainder of the study. At each follow-up visit, diary cards would be reviewed and collected. Patients who experience an asthma exacerbation (symptoms requiring hospitalization or asthma medication excluded by the study protocol) would be withdrawn from the study.

b) Statistical Considerations

Sample size calculations. There are two available options for sample size calculation.

In the first option, sample size calculations would be based on the principles of a non-inferiority study with 90% power to reject the null hypothesis that the test and standard are not equivalent. As asthma is a multifaceted disease, reasonably small differences between the branded product and the generic should also be considered for a range of efficacy and safety variables.

In the second option, sample size calculations would be based on a study in which both the generic product and PULMICORT RESPULES would be statistically significantly superior to placebo and in which the generic product and PULMICORT RESPULES would yield clinically comparable results.

Statistical analysis. Any study must have pre-defined primary and secondary outcome variables. Because this clinical study would be designed to demonstrate efficacy equivalence to

[55] Asthma Treatment Guidelines, *supra* note 7.

PULMICORT RESPULES, the primary outcome variable must be average daytime and nighttime symptom scores over the entire treatment period. However, certain secondary outcome variables are also indicative of efficacy, important for safety, or important for subsequent systemic exposure testing, and should be measured as well. These include:

→ Lung function in those able to do the testing (in general, children 5 years and older)

→ PK measurements in a subset

→ HPA axis assessment in a subset

→ Adverse events

→ Number of asthma exacerbations

→ Nighttime awakenings requiring rescue medication use (*e.g.*, albuterol)

→ Daily rescue medication use

2. Pharmacokinetic Study for Systemic Exposure and Safety Equivalence

As with the efficacy equivalence study, the pharmacokinetic study would need to be designed with certain points in mind:

→ The powering of the PK study would have to be estimated by a follow-on BIS manufacturer based on variability in pilot PK data. Sample size would be based on the expected variability in Cmax and AUC (probably in the range of at least 36 subjects).

→ If a follow-on manufacturer is proposing to manufacture more than one dose strength, then either each generic dose strength needs to be compared with the same dose strength of PULMICORT RESPULES or the company would need to confirm dose proportionality between the various doses of its product (one of which has been shown to be bioequivalent to PULMICORT RESPULES).

The PK study should be a single dose, two-way crossover study of test product vs. PULMICORT RESPULES administered at the same dose in healthy adult subjects. Plasma sampling to determine budesonide concentration would be performed over 12 hours post dose.

E. Alternative 505(b)(2) Approval Mechanism for Follow-on BIS

As noted in Section C.2 above, "proving" BE for a non-systemic product is not really proving BE at all; rather, to "prove" BE for a non-systemic product, FDA looks to certain safety and efficacy surrogate markers for BE that, if met, will demonstrate that there are no significant differences between the test product and the reference product. When an extensive clinical program is required to show this lack of significant differences – when a generic applicant's clinical program must be so complex that it resembles an innovator's Phase III program – the ANDA at issue may have pushed beyond the statutory bounds of the ANDA program.

Under both the statute and the regulations, an ANDA may not include clinical data to demonstrate a drug product's safety and effectiveness.[56] As FDA notes in its preamble to the ANDA final rule, "if clinical investigations are needed to establish a product's safety or effectiveness, that product is not suitable for approval under an ANDA."[57]

FDA addressed this issue in promulgating the final regulations governing ANDA submission. Two of the comments that FDA received on the proposed regulation objected to the inclusion of "well-controlled clinical trials that establish the safety and effectiveness of the product" as one of the approaches permitted for demonstrating bioavailability or bioequivalence, and suggested that applications requiring those clinical trials should be converted to §505(b)(2) applications by the Agency.[58]

In responding to these comments, FDA stated:

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[56] *See* FDCA § 505(j)(2)(A) (delineating the items that shall be contained in an ANDA); *see also* 21 CFR § 314.93(e)(1)(i), 314.93(e)(2) (noting that if information derived from animal or clinical studies is necessary to show that the drug product is safe or effective, then FDA will not approve a suitability petition). Even an ANDA submitted after FDA approval of a suitability petition may only include evidence of "limited confirmatory testing"; that is, data demonstrating that characteristics making the drug different from a listed drug do not alter its safety and effectiveness. 21 CFR § 314.93; *see also* Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17957-58 (Apr. 28, 1992) ("by 'limited confirmatory testing,' FDA means 'simple studies intended to rule out unlikely problems.' Such tests do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective.") *and* Proposed Rule, Abbreviated New Drug Applications, 54 Fed. Reg. 28872, 28880 (July 10, 1989). Together, the Proposed Rule and the Final Rule preambles define parameters of "limited confirmatory testing." These two sections of the preambles are also cited in FDA's Draft 505(b)(2) Guidance, at 4, to define the scope of "limited confirmatory testing."

[57] Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17960 (Apr. 28, 1992). FDA continues by saying "FDA does not, however, interpret this section to preclude the use of data to demonstrate whether a proposed drug product will have the same therapeutic effect as a reference listed drug." FDA's interpretation cannot be read to permit what has been expressly precluded in the prior sentence. No matter the Agency's interpretation regarding, for example, the inclusion of limited confirmatory studies in an ANDA, the fact remains that clinical studies to establish safety and effectiveness are not permitted in an ANDA, and FDA may not bring those studies into an ANDA through a bioequivalence back door.

[58] Final Rule, Abbreviated New Drug Application Regulations, 57 Fed. Reg. 17950, 17977-78 (Apr. 28, 1992). Note that there is a small but significant difference in the applicable regulatory wording that was confused by the commenters. The regulations permit the use of "well-controlled clinical trials that establish the safety and effectiveness of the product" for <u>bioavailability</u> purposes and the use of "appropriately designed comparative clinical trials" for <u>bioequivalence</u> purposes. Under tenets of statutory construction, these two descriptions must mean two different things – thus, "appropriately designed comparative clinical trials" are necessarily something other than "well-controlled clinical trials."

> [T]he statute does not restrict applicants to a specific method for demonstrating bioequivalence. . . . The measurement of clinical endpoints may thus be an acceptable approach for establishing bioequivalence for purposes of ANDA approval. The fact that clinical trial data are submitted to demonstrate bioequivalence does not therefore force FDA to convert an application to a section 505(b) application.[59]

FDA's response to these comments was very carefully worded. It is true that clinical trial data – in particular, data from "appropriately designed comparative clinical trials" – may be submitted as proof of bioequivalence under the regulations and the statute. Therefore, as FDA stated, the mere "fact that clinical trial data are submitted to demonstrate bioequivalence does not . . . force FDA to convert an application." For example, FDA may review limited confirmatory studies as part of an ANDA[60] and has used BE endpoints from clinical trials, as contemplated in the regulations, as the basis for approval of certain generic drug products. However, there are some kinds of clinical data that are so extensive, and that so resemble the results of the Phase III trials required for NDA approval, that inclusion in an ANDA may be untenable.

FDA has been given wide discretion by Congress to determine the best methods of gauging bioequivalence for products that are not intended to be absorbed into the bloodstream.[61] But that discretion must be bounded, at its outer limit, by the overall statutory structure that separates NDAs from ANDAs. Congress has spoken regarding the distinction between NDAs and ANDAs; congressional intent is made clear in the legislative history of the Hatch-Waxman amendments: "Generic copies of any drugs may be approved if the generic is the same as the original drug or so similar that FDA has determined the differences **do not require safety and effectiveness testing**."[62] If ANDAs are approved on the basis of well-controlled clinical trials with safety and efficacy endpoints, even if those trials are characterized as BE studies, then the BE exception could swallow the ANDA rule. When extensive safety and efficacy trial data from well-controlled clinical trials are required to "prove" bioequivalence, it may be more appropriate to convert the application from an ANDA to a § 505(b) application.

Under section 505(b)(2) of the FDCA, an applicant may file an application for a new drug that relies on studies that "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted."[63] By using a § 505(b)(2) application rather than an ANDA, an

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[59] *Id.*

[60] *See supra* note 56.

[61] FDCA § 505(j)(8)(C); *see also Schering Corp. v. FDA*, 51 F.3d 390, 399 (3d Cir. 1995); *Bristol-Myers Squibb Co. v. Shalala*, 923 F. Supp. 212, 217-18 (D.D.C. 1996).

[62] H.R. Rep. No. 98-857, at 14-15 (1984), *reprinted in* 1984 U.S.S.C.A.N. 2647, 2647-68 (emphasis added).

[63] Generally, a § 505(b)(2) application is filed when a "modification of a listed drug . . . for which investigations, other than bioavailability or bioequivalence studies, are essential to the approval" is sought. 21 CFR § 314.54(a). Under the regulations, a § 505(b)(2) application may not be submitted for a drug product whose only difference from the reference listed drug is that

applicant could continue to rely on certain material in AstraZeneca's PULMICORT RESPULES® (budesonide inhalation suspension) NDA but could also conduct clinical studies that demonstrate the safety and efficacy of the follow-on product in a pediatric asthma population. At completion of those studies, FDA would be in possession of the efficacy and safety data necessary to make a full and informed decision regarding whether the follow-on product should come onto the market.

F. Product Quality

Generic drugs must be "manufactured to the same quality standards" as brand name drugs.[64] Although the particular manufacturing specifications applicable to innovator and generic products may differ due to different manufacturing processes or other variables, the manufacturing specifications that apply to the respective products "will have been determined by the agency to be adequate to ensure and preserve the identity, strength, **quality**, purity, and potency of the drug."[65] Indeed, an ANDA may not be approved by the FDA if "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity."[66] Furthermore, FDA recommends that the inactive ingredients in the generic oral inhalation drug product be qualitatively the same and quantitatively essentially the same as the inactive ingredients in the formulation of the reference listed drug. The concentration or amount of the inactive ingredient(s) in a generic formulation should not differ by more than 5% of the concentration or amount in a reference listed drug.[67]

FDA is concerned about product quality because product quality can easily affect product safety and efficacy. "[D]ifferent inactive ingredients can alter the absorption and the efficacy of a particular product."[68] This potential for inactive ingredients and other product quality markers to

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the rate or extent of absorption or availability to the site of action is either intentionally or unintentionally less than that of the reference listed drug. *Id.* § 314.54(b). The intent of this regulation is to prevent a drug that fails bioequivalence testing to be approved through the § 505(b)(2) route. However, the situation at hand is very different. For inhalation suspension products indicated for pediatric asthma control, as has been discussed above, there are complications to assessing bioequivalence. Here, therefore, a proposed generic product has not *failed* a bioequivalence test; rather, there is a limited meaningful ability to assess the bioequivalence of the proposed generic product without full safety and efficacy clinical studies.

[64] FDA White Paper: New FDA Initiative on 'Improving Access to Generic Drugs' (June 12, 2003) *available at* http://www.fda.gov/oc/initiatives/generics/whitepaper.html. *See also* 21 CFR § 320.1(c) (defining "pharmaceutical equivalents" as, in part, drug products meeting "the identical . . . applicable standard of . . . quality, and purity . . ..").

[65] Final Rule, Supplements and Other Changes to an Approved Application, 69 Fed. Reg. 18728, 18749 (Apr. 8, 2004) (emphasis added).

[66] FDCA § 505(j)(4)(A).

[67] Draft Nasal Guideline at 8.

[68] OINDP Transcript at 40 (Comments of Dr. Wallace Adams, PhD, OPS, CDER).

affect a product's safety and efficacy may be particularly pronounced in an inhalation suspension. Further, FDA noted in its final guidance on chemistry, manufacturing, and controls documentation for nasal and inhalation products that:

> Because of the route of administration and the sensitive nature of various patient populations using oral inhalation . . . drug products, more thorough characterization with additional comprehensive controls (*e.g.* strength, quality, purity), as compared to drug products for other routes of administration, should be considered for excipients used in these drug products. Moreover, for nasal and inhalation suspension formulations, additional controls should be applied to critical excipients **to ensure safety and effectiveness of the drug product.**[69]

There are real risks to patients if follow-on BIS product quality is not meticulously assessed. For example:

→ The follow-on product could be less potent than PULMICORT RESPULES® (budesonide inhalation suspension). Inhaled corticosteroid dose reduction can precipitate exacerbation in previously stable patients.[70] Thus, a stable patient taking PULMICORT RESPULES who then receives a sub-potent generic substitute is at risk for asthma worsening, a particular concern in a pediatric population as young as one year old that is unable to report worsening symptoms.

→ The follow-on product could be more potent than PULMICORT RESPULES, resulting in higher systemic exposure. Adverse events associated with the use of inhaled steroids include adrenal gland suppression and bone disorders, like growth suppression and osteoporosis. These and most other side effects of inhaled steroids are dependent on the degree of systemic exposure associated with taking the drug.

→ The follow-on product could contain impurities, extractables, or leachables not found in PULMICORT RESPULES, which could contribute to asthma exacerbation.

Before FDA approved the NDA for PULMICORT RESPULES, AstraZeneca was required to develop and meet very particular and extensive product quality standards.[71] FDA

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[69] Ctr. for Drug Eval. & Research, FDA, *Guidance for Industry: Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products – Chemistry, Manufacturing, and Controls Documentation*, at 7 (July 2002), *available at* http://www.fda.gov/Cder/guidance/4234fnl.pdf (emphasis added).

[70] For example, in one study, 13 out of 50 patients experienced an asthma exacerbation with a 50% reduction in inhaled corticosteroids dose. Jörg D. Leuppi, Cheryl M. Salome, Christine R. Jenkins, Sandra D. Anderson, Wei Xuan, Guy B. Marks, Heikki Koskela, John D. Brannan, Ruth Freed, Morgan Andersson, Hak-Kim Chan & Ann J. Woolcock, *Predictive Markers of Asthma Exacerbation during Stepwise Dose Reduction of Inhaled Corticosteroids*, 163 Am. J. Respiratory Critical Care Med. 406 (2001).

[71] AstraZeneca's interactions with FDA regarding product quality and manufacturing issues are detailed in the PULMICORT RESPULES file, NDA-20-929.

insisted on those product quality standards, and the related manufacturing specifications, because those standards were determined to be essential to the integrity of the product. Subsequent to approval, the quality standards have been further strengthened for certain parameters. Those product quality standards were, and continue to be, important for PULMICORT RESPULES. The same product quality standards are just as important for any potential product using PULMICORT RESPULES as a reference listed drug. Therefore, an appropriate set of specifications for any follow-on BIS product would address, at least, the following characteristics:

- Agglomerates
- API assay
- Appearance
- Color
- Content uniformity
- Disodium edetate assay
- Foreign particles
- Identity of API
- Impurities and degradation products
- Osmolarity
- Particle size distribution
- pH
- Potential leachables
- Sterility

AstraZeneca has discussed all of these characteristics extensively with FDA in the context of PULMICORT RESPULES. All of these characteristics have some effect on safety and effectiveness, and several are discussed in further detail below.

Leachables and Extractables. Drug products packaged in semipermeable containers present particular difficulties regarding leachables and extractables. As indicated in FDA's draft guidance on *Inhalation Drug Products Packaged in Semipermeable Container Closure Systems*,[72] stringent specifications for leachables and extractables are set "to avoid the occurrence of adverse reactions, such as toxicologic, irritant, or immunologic reactions from chemical impurities."[73] The guidance notes that:

> In an inhalation drug product packaged in a semipermeable container, in addition to chemical impurities that can accumulate over time as a result of the degradation of formulation components or leaching from the container closure system, chemical impurities can enter from the local environment. For example, volatile components from the local environment, particularly the secondary packaging, can react with the drug product to form different impurities. . . . As a result of this permeability, chemicals originating from packaging materials, such as adhesives, varnishes, and solvents, have been found in inhalation drug products packaged in LDPE.[74]

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[72] Ctr. for Drug Eval. & Research, FDA, *Guidance for Industry: Inhalation Drug Products Packaged in Semipermeable Container Closure Systems* (July 2002) (draft), *available at* http://www.fda.gov/cder/guidance/4168dft.pdf.

[73] *Id.* at 1-2.

[74] *Id.* at 2.

There are some particular concerns regarding these types of impurities in the asthma patient population: "many of these chemical contaminants are potential respiratory irritants. No previously reported adverse reactions can be conclusively attributed to chemical contaminants. However, given the known sensitivity of these patients to respiratory irritants and sensitizers, it is possible that these chemical contaminants may induce bronchospasm."[75] The guidance notes that prevention of contamination is important in drugs to treat asthma in particular:

> Data indicate that the asthma mortality rate is increasing in the United States. The reason for this increase is unknown but is likely to be caused by a variety of factors. Since it is conceivable that chemical contaminants in the inhalation solutions used to treat the most critically ill asthmatics could play a role, it is important that preventive measures be taken to limit, to the extent practicable, the leaching and entry of chemical contaminants into the drug formulation.[76]

In accordance with this guidance, AstraZeneca has been required to test the plastics, foils, inks, and printing processes that are involved in the PULMICORT RESPULES container system and to set stringent specifications for these, and also to investigate potential degradation or reaction products of impurities. FDA also specifically rejected any use of paper labeling or ink printing on semipermeable containers for PULMICORT RESPULES. Given the importance of reducing impurities, particularly for this sensitive patient population, similar processes must be required for any follow-on BIS packaged in semipermeable containers. These concerns similarly apply regarding impurities and degradation products, discussed in more detail below.

Impurities and Degradation Products. As with the process for leachables and extractables, FDA has required that AstraZeneca extensively test to determine what impurities and degradation products might be present in PULMICORT RESPULES, and then to toxicologically qualify any impurities and degradation products. In fact, FDA has held AstraZeneca to higher standards than are required by the ICH guidelines, particularly regarding potentially genotoxic impurities. For potentially genotoxic impurities or degradation products containing a structural alert, FDA requires specification levels of not more than 0.10% for AstraZeneca inhalation products, unless those impurities or degradation products have been toxiologically qualified.

As with leachables and extractables, FDA has required that AstraZeneca conduct an extensive testing and toxicological qualification program for impurities and degradation products because this is a potential safety issue. Therefore, similar testing standards and similar toxicological qualification processes must be applied for any follow-on BIS product: the follow-on BIS manufacturer must, at a minimum, be required to test its product to determine what impurities or degradants may exist and also be required to characterize any existing impurities or degradants.

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[75] *Id.* at 2-3.

[76] *Id.* at 3.

Sterility. Because the FDA stressed the importance of sterility testing, AstraZeneca has extensively examined both the sterilization process used and the potential impurities or degradation products that may result from use of heat sterilization.

Mass Median Diameter and Particle Size Distribution. The particle size distribution in suspension formulations has the potential to influence the rate of dissolution and the extent of drug availability to the sites of action in the lungs and to the systemic circulation. AstraZeneca has been held to tight specifications for this parameter.

Although the exact specifications regarding particle size will be based on the actual data provided by the follow-on product manufacturer, the particle size and the particle size distribution within the suspension will influence the amount and distribution of drug in nebulized droplets of different sizes. This, in turn, will influence the amount of drug delivered to the site of action in the lung. A wider range of particle sizes, and particularly a larger proportion of large particles, will result in a lower delivery of drug to the lungs, and thus in a reduced clinical efficacy. In short, lung delivery of a drug is strongly dependent on particle size. Therefore, a tight control of the particle size distribution specification is essential to ascertain consistent efficacy and safety within various batches of the same product, as well as comparable efficacy and safety between a test product and a reference product. This is in contrast to a nasal formulation, where a wider range of particle sizes would have less dramatic effects on the delivery to the site of action, given that both large and small particles can easily and directly reach the site of action, the nasal passages.

Agglomerates. Similarly, as for the particle size distribution, the presence and extent of agglomerates may be important for the availability of the drug – presence of agglomerates may influence the amount and distribution of drug in the nebulized droplets of different sizes, and may have consequences on efficacy and safety, as discussed above. For this parameter, AstraZeneca has been required to conduct extensive characterization and enumeration testing to support the finished drug product specification.

Container closure system. The shape and volume of the primary container may potentially have an impact on the drug product stability profile under various storage and transportation conditions. To respond to these concerns, AstraZeneca has been required to thoroughly investigate and optimize the primary container design, ensuring that the dispensed dose from each PULMICORT RESPULES ampule falls within certain specifications, even when subjected to transportation simulation studies.

Because of AstraZeneca's extensive experience on this issue, AstraZeneca strongly believes that for any new follow-on BIS product launched, the manufacturer should assess the transportation effect on the product, particularly as related to the container closure system. AstraZeneca examined the IVAX container closure system available in Italy. Our investigation suggests that the ampule of that product is not optimized with regard to shape and volume, with resulting negative effects on the IVAX product drug stability profile. Specifically, AstraZeneca conducted a transport simulation study on the IVAX product and observed a resulting decrease of about 20% in dispensed dose. It must be emphasized that this is the result of a single test.

If IVAX intends to use the same container in the United States that it is using for its Italian product, then this container closure issue should be assessed by IVAX and reviewed by FDA prior to product approval. Further, FDA should require that all potential manufacturers of follow-on BIS products assess transportation effects on the products, particularly as related to the container closure system.

In summary, although product quality is always an important factor in FDA's drug approval process, it has particular importance for an inhalation suspension product. The entire product quality profile – including excipients, inactive ingredients, specification requirements, and manufacturing processes – is acknowledged to be important to the product's ultimate safety and efficacy.[77] This is precisely why FDA required AstraZeneca to scrutinize and characterize its manufacturing processes and specifications so meticulously. If, as FDA has consistently insisted, that scrutiny and quality control is important for the innovator, it is important for everyone, including follow-on BIS manufacturers. Therefore, as part of its ANDA approval, any follow-on BIS manufacturer should be required to meet equivalent product quality standards.

III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from preparation of an Environmental Assessment or an Environmental Impact Statement under 21 CFR § 25.31.

IV. ECONOMIC IMPACT

This information will be submitted if requested by the Commissioner.

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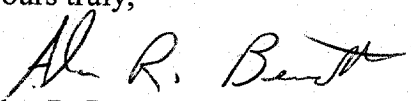
[77] *See supra* note 69.

V. CERTIFICATION

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

Yours truly,



Alan R. Bennett

ARB:pjz
Enclosures

cc: Mr. Gary Buehler (via Hand Delivery)
Ms. Elizabeth Dickinson (via Hand Delivery)
Dr. Dena Hixon
Dr. Dale Conner
Ms. Jane Axelrad
Dr. John Jenkins
Dr. Robert Temple
Dr. Robert Meyer
Dr. Badrul Chowdhury

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