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September 18, 2008

BY HAND

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

Re: Citizen Petition Concerning Approval of Follow-On Budesonide Inhalation Suspension Products (Docket No. 2006P-0242)

Dear Sir or Madam:

On behalf of AstraZeneca LP ("AstraZeneca"), I am writing to supplement the above-referenced citizen petition that was filed on June 9, 2006. In that petition, AstraZeneca requested the Food and Drug Administration ("FDA") to refrain from approving any follow-on budesonide inhalation suspension product ("follow-on BIS") using PULMICORT RESPULES® as a reference listed drug ("RLD") unless that approval is supported by appropriate legal, scientific and procedural methodologies. In light of two very recent developments at FDA that are highly relevant to the actions requested in AstraZeneca's citizen petition, AstraZeneca is herewith submitting this supplemental letter along with supporting documentation.

A. The July 23, 2008, Meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology on Bioequivalence of Inhalation Drug Products

In its citizen petition, AstraZeneca demonstrated that approval of follow-on BIS products under Section 505(j) of the FDCA, 21 U.S.C. § 355(j), raises significant and difficult questions concerning the bioequivalence of follow-on BIS products to PULMICORT RESPULES. Given these difficulties, AstraZeneca set forth a comparative safety and effectiveness program that should be undertaken in lieu of bioequivalence studies for follow-on BIS products. Such a program would, at a minimum, need to include a 12-week clinical trial between the test and reference products to provide reliable estimates of "equivalent effectiveness." It would also need to include a PK study to assess bioequivalence of systemic exposure as a surrogate for long-term safety effects such as growth suppression.

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AstraZeneca believes that a recent meeting of the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology further highlights the need for such a program to evaluate the safety and efficacy of follow-on BIS products. Specifically, on July 23, 2008, that Advisory Committee considered bioequivalence issues involving inhalation drug products. In describing the need for this meeting, FDA declared that "no validated methods [for measuring potency] with acceptable sensitivity and precision are available" for inhaled corticosteroid products.[1] Thus, just as AstraZeneca explained in its citizen petition, FDA indicated that more information is needed about what types of studies may be relied upon to evaluate the bioequivalence of proposed generic versions of inhaled corticosteroid products.

Moreover, during the Advisory Committee meeting, a generic manufacturer indicated that detailed studies are needed to determine the bioequivalence of an inhaled corticosteroid generic product to an RLD. Speaking on behalf of Teva Pharmaceuticals, Dr. Paul Dorinsky (Vice-President of Global Respiratory Clinical Research) stated that no endpoint has been able to reproducibly be used to establish dose response for inhaled corticosteroids. Taking into account that conclusion, Teva proposed a three part clinical program: (1) a clinical pharmacology study for each dose to establish equivalence for AUC and Cmax; (2) a clinical efficacy study involving adults and adolescents of 12 weeks or longer using an established efficacy measure as the primary endpoint, with extrapolation of the results to children; and (3) a clinical safety study (or PK study) that evaluates the test and reference product to show comparable safety for children.[2]

AstraZeneca does not agree that such studies are sufficient to measure the bioequivalence of inhaled corticosteroid products, including follow-on BIS products. Nevertheless, FDA's statements and Teva's testimony at this recent Advisory Committee meeting do provide further evidence that follow-on BIS products should not be the subject of abbreviated new drug applications ("ANDAs") in the first place.[3] As AstraZeneca discussed in its petition, when an extensive clinical program must be undertaken to ensure that there are no significant differences between a generic product and an RLD, the proposed generic product may cross the line and no longer be eligible for approval through an ANDA under Section 505(j) of the FDCA. Rather, in such cases, the appropriate route for approval is through submission of a new drug application ("NDA") either under Section 505(b)(1) or 505(b)(2) of the statute and, as such, FDA may not assign an AB rating to any follow-on BIS product.

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[1] *See* Briefing Information, Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, Food and Drug Administration, available at http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4370b1-01-FDA.pdf.

[2] *See* Testimony of Dr. Paul Dorinsky, Teva Pharmaceuticals, before the Advisory Committee for Pharmaceutical Science and Clinical Pharmacology, July 23, 2008, available at http://www.fda.gov/ohrms/dockets/ac/08/slides/2008-4370s2-07-OPH-Dorinsky_files/frame.htm.

[3] This is especially true in light of Teva's reference to the need for a clinical safety study (or PK study) to show comparable safety for children of the generic product and the listed drug.

Although FDA has taken the position that "limited confirmatory studies" may be submitted in support of an ANDA, it can hardly be said that the types of studies proposed by Teva or required to measure bioequivalence of inhaled corticosteroids would be allowed under that exception. Indeed, when FDA established this exception, it stated that "limited confirmatory testing" means "simple studies intended to rule out unlikely problems" and "such tests do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective." 54 Fed. Reg. 28872, 28880 (July 10, 1989). Moreover, as AstraZeneca demonstrated in its petition, the fact that Congress provided FDA with broad discretion to measure bioequivalence for non-systemic products does not mean that FDA may ignore the statutory prohibition against reliance on substantial clinical data in an ANDA. *Compare* 21 U.S.C. § 355(j)(8)(C) and 21 U.S.C. § 355(j)(2)(A).

Finally, given the significant uncertainties surrounding the adequacy of measures to assess bioequivalence of inhalation drug products discussed at the Advisory Committee meeting, AstraZeneca reiterates the need for a guidance document that addresses such issues before any ANDAs involving PULMICORT RESPULES are approved. As Teva itself acknowledged during the Advisory Committee meeting, there is a strong need for scientifically-based guidelines to be issued by FDA on bioequivalence of inhalation drug products. In fact, since FDA has not previously communicated its regulatory approach to addressing bioequivalence of inhalation drug products and given the complex scientific issues that are involved, a "Level 1" guidance document would appear to be required under FDA's regulations governing good guidance practices. 21 C.F.R. § 10.115(c). As a Level 1 document, a draft of such a guidance, including any potential draft product specific recommendation, should be made available for public review and comment, and the final guidance should incorporate suggested changes as appropriate. 21 C.F.R. § 10.115(g)(1).[4]

B. The July 28, 2008, Decision of FDA to Deny a Citizen Petition Relating to Carve-Outs of Labeling for Generic Irinotecan Hydrochloride Products

In its citizen petition, AstraZeneca also demonstrated that the labeling proposed by IVAX Pharmaceuticals ("IVAX") for its follow-on BIS product is legally impermissible. Specifically, based on a proposed label that IVAX disclosed publicly, IVAX has proposed to eliminate certain once-daily references from its labeling so that its generic product would purportedly only provide for twice-a-day dosing. As explained in its citizen petition, AstraZeneca does not

[4] A guidance document for inhalation drug products would, of course, be consistent with FDA's earlier actions to develop guidance on bioavailability and bioequivalence studies for nasal aerosols and nasal sprays *See* Guidance for Industry, Bioequivalence and Bioavailability Studies for Nasal Aerosols and Nasal Sprays for Local Action (Draft), April 2003, available at http://www.fda.gov/cder/guidance/5383DFT.pdf.

believe that, based on IVAX's proposed label, FDA may approve the IVAX generic product. AstraZeneca submits that IVAX's public label still instructs once-daily dosing, through at least its instructions to titrate patients to the lowest effective dose once asthma stability is achieved. Moreover, even if FDA were to permit IVAX to remove all instructions for once-daily dosing from its label, FDA may still not approve the generic product under the FDCA and the agency's own regulations.

The FDA has issued regulations that allow for differences in labeling as long as they do not "render the proposed [generic] drug product less safe or effective than the listed drug for all remaining, non-protected conditions of use."[5] 21 C.F.R. § 314.127(a)(7). On July 28, 2008, FDA clarified how it will apply the standard enunciated in these regulations to situations where an attempted labeling carve-out would be based on a method of use patent. In its recent decision involving Camptosar® (irinotecan hydrochloride), FDA decided that the carve-out of a patent-protected first line combination use of the product would not render the generic product less safe and effective than the listed drug for the non-patent-protected second line of use as a monotherapy.[6] In making that determination, FDA rejected the petitioner's argument that the agency must refuse to approve ANDAs under its regulations since the product would, in fact, be used as a first line combination use as a result of state mandatory substitution laws and forseeable off-label use of the product.

AstraZeneca wishes to emphasize that FDA's decision on carve-outs for generic irinotecan hydrochloride products is fundamentally different from the situation involving PULMICORT RESPULES. In contrast to the Camptosar matter where FDA was faced with two different indications, only one indication is involved in the case of PULMICORT RESPULES. The product has only been approved for the treatment of pediatric asthma. Moreover, FDA reached its conclusion in the Camptosar matter after observing that the labeling for a generic irinotecan hydrochloride product would be essentially the same as the labeling with which Camptosar was originally approved and marketed for four years (i.e., as a monotherapy). In contrast, when PULMICORT RESPULES was approved, its labeling provided for both once-a-day and twice-a-day administration for the same indication. The product has never been marketed with just a twice-a-day dosing instruction.

In its Camptosar decision, FDA also clarified that it will only compare the labeled uses of the proposed generic product and the RLD. In this context, AstraZeneca notes that the lowest dosage strength in the IVAX generic product, as in PULMICORT RESPULES, would be 0.25

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[5] AstraZeneca does not concede that FDA's regulations (21 C.F.R. § 314.94(a)(8)(iv) and § 314.127(a)(7)) as applied to the situation involving PULMICORT RESPULES are permissible as a matter of law under the FDCA.

[6] *See* Letter from Janet Woodcock, Director, Center for Drug Evaluation and Research, to Ernest Lengle, Watson Laboratories, Docket No. 2008-P-0069, July 28, 2008.

mg. If IVAX's product were only labeled for administration twice a day, the lowest daily dose it would provide is 0.5 mg/day—that is, 0.25 mg twice a day. On the other hand, since the labeling for PULMICORT RESPULES provides for once-a-day dosing, the lowest daily dose for this drug product is 0.25 mg administered once per day. Based on recent data, more than 10% of prescriptions for PULMICORT RESPULES -- prescriptions involving tens of thousands of children -- were written for a dose of 0.25 mg administered once per day. And, almost 30% of all prescriptions for 0.25 mg doses of PULMICORT RESPULES were written for once-a-day administration.[7]

In light of this information, FDA cannot conclude under its regulations that the IVAX generic product would be as safe as PULMICORT RESPULES if its label were to provide only for twice-daily dosing.[8] Both FDA and NIH have expressed serious concerns about the effects that inhaled corticosteroids, such as budesonide, have on the growth rate of children and on other systemic parameters such as adrenal axis function. In 1998, FDA imposed a safety labeling requirement that, among other things, recommended that systemic exposure to such products should be limited by titrating all patients down to the lowest effective dose once asthma stability is achieved. At the same time, under the auspices of the National Heart, Lung and Blood Institute, the National Asthma Education and Prevention Program has issued expert guidelines recommending that physicians "step down" their patients "to the least medication necessary to maintain control." These recommendations, like those of FDA, were grounded in the recognition that inhaled corticosteroids are safer for patients at lower doses and for shorter periods of time. Hence, it is vitally important that children not receive larger doses of inhaled corticosteroid products than are necessary to control their disease.

In the aftermath of FDA's clarification in the Camptosar decision, there are other potentially significant clinical consequences that the agency would need to consider if IVAX were to successfully remove once-daily dosing from its label. Once-daily treatment with PULMICORT RESPULES results in better patient compliance than does twice-daily treatment.[9] Improved patient compliance rates, in turn, lead to more effective asthma control during long-

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[7] In the course of defending its patents in litigation with IVAX, AstraZeneca recently collected and analyzed prescription data from March 2006 to February 2007 for asthmatic patients aged 0 to 8 years old that have filled at least one prescription for PULMICORT RESPULES. From those data, the total number of prescriptions for once, twice and three times a day administration of PULMICORT RESPULES was calculated. These calculations were conducted for each of the two strengths of PULMICORT RESPULES (0.25mg and 0.5mg), as well as for both together.

[8] In the Camptosar matter, FDA rejected the argument that a product is not safe because of potential off-label use. The agency cannot turn around and rely on potential off-label use to assure itself of the safety of a generic product.

[9] *See* James Kemp et al., *Once Daily Budesonide Inhalation Suspension for the Treatment of Persistent Asthma in Infants and Young Children*, 83 ANNALS ALLERGY ASTHMA IMMUNOLOGY 231, 231 & 238 (Sept. 1999); Bernard S. Bloom, *Daily Regimen and Compliance with Treatment*, 323 Brit. Med. J 647 (22 Sept. 2001).

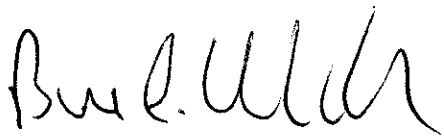
term treatment and may not require use of the product over as long a period of time.[10] Thus, because PULMICORT RESPULES achieves higher patient compliance rates through its once a day dosing regimen, it is likely to result in more effective long-term control of asthma than the IVAX generic product, which IVAX proposes would only provide for dosing twice-a-day. This is significant because, based on recent data, 30% of all prescriptions for PULMICORT RESPULES provided for once-daily treatment.[11]

AstraZeneca respectfully requests that the supplemental information contained in this letter and the attached documents be included in the docket (Docket No. 2006P-0242) and that FDA consider this information in connection with its review of AstraZeneca's citizen petition. AstraZeneca believes that this information provides additional support for FDA to take the actions requested in the citizen petition.

I certify that, to my best knowledge and belief: (a) I have not intentionally delayed submission of this document or its contents; and (b) the information upon which I have based the action requested herein first became known to me and my client on or about July 23, 2008. If I received or expect to receive payments, including cash and other forms of consideration (other than by virtue of our retention by our client) to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: none. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this supplemental information.

Thank you for your consideration of this information.

Respectfully submitted,



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[10] *See* e.g., Brian J. Lipworth, *Airway and Systemic Effects of Inhaled Corticosteroids in Asthma*, 9 PULMONARY PHARMACOLOGY 19-27 (1996).

[11] *See supra* note 7.