DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

WRITTEN REQUEST – AMENDMENT 5

NDA 20-983

GlaxoSmithKline
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Attention: Patrick Wire, Pharm. D.
Director, Regulatory Affairs

Dear Dr. Wire:

Please refer to your correspondence dated April 14, 2005, requesting changes to FDA's December 31, 2005, Written Request for pediatric studies for Ventolin HFA (albuterol sulfate) metered-dose inhaler.

We have reviewed your proposed changes and are amending the Written Request. For convenience, the full text of the Written Request, as amended, follows. This Written Request supersedes the Written Request dated November 18, 2004.

Type of Studies:

In addition to the following clinical studies, you must characterize the dose delivery from the inhaler with two different U.S.-marketed spacers with *in vitro* studies.

Study 1: Safety and efficacy of Ventolin HFA for treatment of obstructive airway disease in children from 2 to <4 years.

Study 2: Safety and efficacy of Ventolin HFA for treatment of obstructive airway disease in children from birth to <2 years.

Study 3: Safety and efficacy of cumulative-dose administration of albuterol sulfate inhalation solution delivered via nebulization or albuterol sulfate HFA inhalation aerosol with a valve holding chamber with attached facemask for the treatment of reversible obstructive airway disease in children from birth to <2 years.

Objective/Rationale:

Study 1: Assess the safety and efficacy of Ventolin HFA delivered with facemask and two different spacers in children with obstructive airway disease between the ages of 2 to <4 years.

Study 2: Assess the safety and efficacy of Ventolin HFA delivered with facemask and spacer in children with obstructive airway disease between the ages of birth to <2 years.

Study 3: Assess the safety and efficacy of cumulative-dose administration of either albuterol sulfate inhalation solution delivered via nebulization or albuterol sulfate HFA inhalation aerosol with a valve holding chamber with attached facemask, in an acute bronchodilation setting in children with obstructive airway disease from birth to <2 years of age.

Indications to be Studied:

Studies 1 and 2: Treatment and prevention of bronchospasm in children from birth to <4 years of age with obstructive airway disease.

Study 3: Treatment or prevention of bronchospasm in children from birth to <2 years of age with obstructive airway disease.

Study Design:

Studies 1 and 2: The studies must be randomized, double-blind, placebo-controlled, parallel-group design. Evaluate two doses of Ventolin HFA and placebo in each study. In Study 1 evaluate the adult dose of Ventolin HFA and a lower dose. The results of Study 1 will guide you in selecting the two Ventolin HFA doses for Study 2. The study medication should be administered to all patients on a fixed schedule, either three times daily or four times daily. Treat patients for at least 4 weeks. The use of rescue inhaled or systemic corticosteroids, additional doses of $beta_2$-agonists, and discontinuation due to worsening respiratory symptoms should be allowed and tracked as part of the study design.

Study 3: The study must be a randomized, double-blind, parallel-group design with at least two treatment arms: albuterol inhalation solution 0.63 mg and albuterol inhalation solution 1.25 mg. Administer the dose cumulatively every 20 minutes for the first hour, and then hourly for the next 2 hours. Indicate in the protocol that patients who do not clinically require further dosing after any dose may be excluded from further treatment. However, enrollment must be sufficient to ensure that at least 30 patients per treatment arm complete a minimum of 3 doses of study medication. Data, including medication administration and safety and efficacy parameters as outlined, will be collected for the entire 3 hour treatment period.

OR

The study must be a randomized, double-blind, parallel-group design with at least two treatment arms: albuterol sulfate HFA inhalation aerosol with a valve holding chamber with attached facemask, 180 µg (2 actuations) and 360 µg (4 actuations). Administer the dose cumulatively every 20 minutes for the first hour, and then hourly for the next 2 hours. Indicate in the protocol that subjects who do not clinically require further dosing after any dose may be excluded from further treatment. However, enrollment must be sufficient to ensure that at least 30 subjects per treatment arm complete a minimum of 3 doses of study medication. Data, including medication administration and safety and efficacy parameters as outlined, will be collected for the entire 3-hour treatment period.

Age Groups to be Studied:

Study 1: Patients between the ages of 2 and <4 years. Approximately half of the study patients in each treatment group must be below 3 years of age.

Studies 2 and 3: Patients between the ages of birth and <2 years. A reasonable number of patients below 1 year of age, including neonates, must complete the study.

Number of Patients to be Studied:

Studies 1 and 2: A minimum of 20 patients per arm per study must complete the studies. Approximately one-half of the study patients in each arm must use one type of U.S.-marketed spacer and mask, and the other half must use a different type of U.S.-marketed spacer and mask.

Study 3: A minimum of 30 patients per arm must complete the study.

Entry Criteria:

Study 1: Children between the ages of 2 to <4 years who are suitable candidates for chronic bronchodilator treatment.

Study 2: Children between the ages of birth to <2 years who are suitable candidates for chronic bronchodilator treatment.

Study 3: Children between the ages of birth to <2 years experiencing acute bronchospasm.

Clinical Endpoints:

Studies 1 and 2: The primary efficacy endpoint must include a parental scoring of asthma symptoms, such as wheeze, dyspnea, tightness in the chest, and cough. Other efficacy parameters must include use of rescue medications and treatment failures. The safety assessment must include adverse events (especially assessment of signs and symptoms of adrenergic stimulation), vital signs, ECGs (including measurement of QTc interval), and laboratory tests for blood glucose and serum potassium levels. In Study 1, attempt to measure peak expiratory flow rate as an efficacy endpoint.

Study 3: The primary efficacy endpoint must include clinical scoring of asthma symptoms. The safety assessment must include adverse events (especially signs and symptoms of adrenergic stimulation), vital signs, physical examination, continuous ECG monitoring, and laboratory tests for blood glucose and serum potassium levels.

Study Evaluations:

Studies 1 and 2: Measure the primary efficacy assessment at baseline and throughout the study. Instruct parents or caregivers to record asthma symptoms and adverse events (e.g., signs and symptoms of adrenergic stimulation) on diary cards. Conduct clinic visits approximately weekly. During clinic visits, record vital signs, assess for adverse experiences, and assess for adrenergic stimulation. Perform physical examinations near the beginning and end of the study. Perform

ECGs (including QTc interval) or 24-hour Holter monitoring at the first dosing visit and at a visit toward the end of the treatment period. At both of these visits, ECGs should be performed pre-dose and post-dose, at the expected T_{max}. Perform clinical laboratory measures for blood glucose and serum potassium at baseline and at the end of the treatment period (at the approximate time of expected maximal effect following dosing). Laboratory assessment within 3 months of baseline will be acceptable for the baseline assessment. The primary efficacy variable must be a comparison between active treatment and placebo on the mean change in asthma symptom scores from baseline to the end of the study. In Study 1, attempt to record peak expiratory flow rate twice daily in patients able to do this maneuver.

Study 3: The primary objective of this study is the safety assessment of cumulative doses of albuterol sulfate inhalation solution delivered via a nebulizer or albuterol sulfate HFA inhalation aerosol with a valve holding chamber with attached facemask when used in an acute bronchodilation setting. Record vital signs, assess adverse events, and assess adrenergic stimulation after each dose. Perform physical examinations and clinical laboratory measures for blood glucose and serum potassium at baseline and at the end of the treatment period. Perform continuous ECG monitoring during the entire treatment period. The efficacy endpoint (i.e., asthma symptom scores) should also be determined during the period of cumulative dosing. Compare the two doses in terms of percent improvement from baseline in asthma symptoms scoring after cumulative dosing.

Drug Information:

Study 1: Use Ventolin HFA in conjunction with two different U.S.-marketed spacers. The spacers must not replace the actuator of the inhaler. Approximately one-half of the patients in Study 1 must use one kind of spacer, and the other half must use a different kind of spacer. Use facemasks with the spacers.

Study 2: Use Ventolin HFA in conjunction with a single type of U.S.-marketed spacer. The spacer must not replace the actuator of the inhaler. Use facemasks with the spacers.

Study 3: Use albuterol sulfate inhalation solution via a single type of U.S.-marketed nebulizer or use albuterol sulfate HFA inhalation aerosol repeatedly via a valved holding chamber with attached facemask.

Safety Concerns:

The safety of albuterol sulfate in patients between birth to <2 years is unknown. Other than pharmacologically related adverse effects, such as tremors, no unique adverse events are anticipated.

Statistical Information:

Studies 1 and 2: Analyze the data by analysis of variance or by an appropriate statistical test for the data.

Study 3: Analyze the efficacy data by analysis of variance or by an appropriate statistical test for the data. Describe the number of patients per treatment group that did not require full cumulative treatment. Perform summary statistics for the safety parameters.

Labeling That May Result from the Studies:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

Format of Reports to be Submitted:

Full study reports not previously submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

Timeframe:

Full study reports of the above studies must be submitted to the Agency on or before October 1, 2007, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act. Please remember that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY" in large font, bolded type at the beginning of the cover letter of the submission. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. In addition, send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

In accordance with section 9 of the Best Pharmaceuticals for Children Act, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

1. the type of response to the Written Request (complete or partial);

2. the status of the supplement (withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, approvable, not approvable); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at http://www.fda.gov/cder/pediatric/Summaryreview.htm and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (http://clinicaltrials.gov & http://prsinfo.clinicaltrials.gov/). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site http://prsinfo.clinicaltrials.gov/.

Effective August 29, 2005, **ALL** regulatory submissions, whether sent by U.S. Postal Service, overnight mail service, or courier, should be sent to the following address. Processing of submissions sent to other addresses may be delayed.

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call Ms. Akilah Green, Regulatory Management Officer, at 301-827-5585.

Sincerely yours,

{See appended electronic signature page}

Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Meyer

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