DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 021936

WRITTEN REQUEST

Boehringer Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Rd.
P.O. Box 368
Ridgefield, CT 06877-0368

Attention: Amy Van Andel, DVM, MPH
Director, Regulatory Affairs

Dear Dr. Van Andel:

Reference is made to your October 19, 2015, Proposed Pediatric Study Request for Spiriva Respimat (tiotropium bromide) Inhalation Spray.

BACKGROUND:

These studies investigate the potential use of tiotropium bromide inhalation solution delivered by the Respimat device for the treatment of asthma in children < 12 years of age not adequately controlled on inhaled corticosteroids (ICS). Asthma is a chronic inflammatory disorder of the airways and a leading chronic disease in children; however, as a chronic recurring disease, it is not a diagnosis that can be made in neonates. According to the 2012 National Health interview Survey Data, asthma affected more than 25 million people in the United States and among those were 6.8 million children and adolescents < 18 years of age.

Approved medications used to control asthma in children < 12 years of age include single-ingredient ICS, fixed dose ICS and long-acting beta$_2$-agonist (LABA) combination products, single ingredient LABAs + single ingredient ICS, and leukotriene modifiers and antagonists. Tiotropium bromide is an anticholinergic approved as a capsule for dry powder inhalation for the treatment of chronic obstructive pulmonary disease (COPD) and as an aqueous solution for oral inhalation via the Respimat device for the treatment of COPD and, more recently, for asthma. Tiotropium bromide inhalation solution is the only anticholinergic approved for asthma and is indicated as a bronchodilator for the maintenance treatment of asthma in adult and adolescent patients 12 years of age and older. Although LABAs are also approved as bronchodilators for the maintenance treatment of asthma, safety concerns limit their use to combination therapy with an ICS.

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As a result, the studies outlined in this Written Request are those whose study reports have not previously been submitted to the FDA, but remain highly relevant to the evaluation of the safety and efficacy of tiotropium inhalation solution in the pediatric population for which tiotropium inhalation solution is not yet approved (< 12 years of age). These include a large one-year safety and efficacy study in pediatric patients 6-11 years of age with moderate asthma and an *in vitro* characterization study to assess the effect of using a spacer/valved holding chamber on the delivery of tiotropium (this type of study is desirable to inform health care practitioners of the delivery characteristics of the device when given through a spacer device as would be the case if administered "off label" to a young child). Neonates are not included in this Written Request because asthma, as a chronic recurring disease, cannot be diagnosed in neonates.

Thus, to obtain needed pediatric information on tiotropium bromide inhalation solution, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*:

  Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

  However, because drug delivery information through a spacer is desirable to inform health care practitioners of the delivery characteristics of the device when given through a spacer device as would be the case if administered "off label" to a young child, an *in vitro* characterization study to assess the effect of using a spacer/valved holding chamber on the delivery of tiotropium is required.

  Study 1: An *in vitro* characterization study of the dose delivery from the Respimat inhaler with at least one U.S.-marketed spacer

- *Clinical studies:*

  Study 2: A double-blind, randomized, parallel group, placebo-controlled, efficacy and safety study in children ages 6 to 11 years with asthma who are symptomatic despite maintenance therapy with

a stable medium-dose ICS either alone or in combination with another controller medication (e.g, LABA or leukotriene modifier). The duration must be at least 48 weeks, and the study must include at least two doses of tiotropium bromide inhalation solution.

- *Objective of each study:*

Study 1: To evaluate the particle size distribution of the dose delivered into a cascade impactor from each of the Respimat/spacer combinations and the Respimat alone following a specified number of actuations. The study should include an evaluation of factors that might affect the test results and be of potential importance in the clinical setting.

Study 2: To demonstrate the efficacy and safety of tiotropium bromide inhalation solution delivered once daily over 48 weeks, compared to placebo, in children 6 to 11 years of age with moderate persistent asthma not adequately controlled on medium-dose ICS.

- *Patients to be Studied:*

  - *Age group in which study(ies) will be performed*:
    - Study 1: Not applicable
    - Study 2: Children aged 6 to 11 years of age

  - *Number of patients to be studied:*
    - Study 1: Not applicable
    - Study 2: A minimum of 125 patients per treatment group (2 or more groups) must be randomized and treated with at least one dose of study treatment.

Representation of Ethnic and Racial Minorities: Study 2 must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study 2 endpoints:*

  ☐ *Efficacy Endpoints:*
    - ☐ The primary efficacy endpoint will be the peak FEV1 response within 3 hours post dosing determined at the end of the 24-week treatment period as assessed by spirometry conducted according to American Thoracic Society and European Respiratory Society (ATS/ERS) criteria.
    - ☐ Important secondary endpoints will include pre-dose trough FEV1 at the end of the 24-week treatment period. Other efficacy variables must include other spirometric measures, asthma control, quality of life, rescue medication use, AM and PM pre-dose PEF, asthma symptom scores, and asthma exacerbations.
    - ☐ Measures of compliance will include recording of each home dose administration in an electronic diary.

  ☐ *Safety Endpoints:*

- ☐ Safety outcomes must include adverse events, vital signs (heart rate and blood pressure), physical exam, clinical labs (hematology, chemistry), and 12-lead ECG.

- *Known Drug Safety concerns and monitoring:*
  Safety concerns include class effects of anticholinergic drugs such as decreased secretions leading to dry mouth, urinary retention, and worsening of narrow angle glaucoma. Monitoring for safety concerns will be performed in the clinical trial as listed under Safety Endpoints above.

- *Extraordinary results:*
  In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
  - *dosage form:* aqueous solution delivered via the Respimat Soft Mist inhaler device
  - *route of administration:* oral inhalation
  - *regimen:* two inhalations once daily

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate

formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any pediatric formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*
Efficacy analyses and summary of safety data must be based on all randomized patients that received at least one dose of trial medication.

  Study 2: Based on a two-group t-test with a power of 80%, a probability of a type I error of 2.5% (one-sided), and assuming a common SD of 0.340 L for the primary endpoint of FEV_1 $peak_{0\text{-}3h}$, 127 patients per group would be required in order to detect a difference between treatment groups of 0.120 L.

  The efficacy endpoints must be FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 response, and each should be analyzed using a REML-based MMRM with terms for 'treatment', 'country', 'visit', 'treatment-by-visit interaction' as categorical effects and 'baseline', 'baseline-by-visit-interaction' as continuous covariates as well as 'patient' as a random effect. Multiplicity should be addressed using a hierarchical testing procedure to establish efficacy as follows:
    - FEV_1 $peak_{0\text{-}3h}$ response with tiotropium bromide inhalation spray 5 mcg/day > FEV_1 $peak_{0\text{-}3h}$ response with placebo
    - FEV_1 $peak_{0\text{-}3h}$ response with tiotropium bromide inhalation spray 2.5 mcg/day > FEV_1 $peak_{0\text{-}3h}$ response with placebo
    - Trough FEV_1 response with tiotropium bromide inhalation spray 5 mcg/day > trough FEV_1 response with placebo
    - Trough FEV_1 response with tiotropium bromide inhalation spray 2.5 mcg/day > trough FEV_1 response with placebo

  If any of the steps are not statistically significant at the 0.025 (one-sided) level of significance, analyses of the subsequent steps will be considered descriptive.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that tiotropium bromide inhalation solution is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should 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, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

  Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before October 30, 2016. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) 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.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please 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. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please 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.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Jessica Lee, Regulatory Project Manager, at (301) 796-3769.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
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/

CURTIS J ROSEBRAUGH
02/12/2016