CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021936Orig1s000

PHARMACOLOGY REVIEW(S)

Secondary Pharmacology and Toxicology Review for NDA 21-936

TO: NDA 21-936 (Boehringer Ingelheim)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: September 3, 2014

Overview: I concur with the recommendation of Dr. Luqi Pei (detailed in a nonclinical review dated August 26, 2014) that the pharmacology and toxicology of Spiriva Respimat has been adequately studied and the drug product should be approved from a nonclinical perspective.

Spiriva Respimat, a tiotropium bromide (anticholinergic) metered-dose inhaler, is indicated for the treatment of bronchospasm and dyspnea associated with COPD. The proposed maximum recommended daily clinical dose of Spiriva Respimat is 5 µg/day. The nonclinical safety program of Spiriva Respimat is based upon complete tiotropium pharmacology and toxicology studies that were previously submitted and reviewed under an existing NDA for Spiriva HandiHaler (NDA 21-395), a tiotropium dry powder inhaler.

The original NDA 21-936 application was submitted on September 16, 2007. No outstanding issues were identified by the nonclinical review (dated July 29, 2008). The application received a Complete Response on September 16, 2008, for clinical deficiencies, and a resubmission was received March 24, 2014. No new, significant nonclinical data was included in the current submission, so a detailed pharmacology and toxicology review of Spiriva Respimat was not needed for this NDA.

Labeling: Changes to Section 8.1 (Pregnancy), Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility), (b) (4) were proposed in Dr. Pei's review dated August 26, 2014. As clinical PK data indicate Respimat (5 µg) and HandiHaler (18 µg) produce similar tiotropium exposure levels, Dr. Pei recommended retaining HandiHaler animal:human exposure ratios for Respimat labeling. In addition, Dr. Pei recommended removing animal reproduction data (b) (4) per current labeling practice. I agree with Dr. Pei's labeling recommendations. See Dr. Pei's review for complete product labeling details.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/

MARCIE L WOOD
09/03/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 21-936
Supporting document/s:	Sequence 0003
Applicant's letter date:	March 24, 2014
CDER stamp date:	March 24, 2014
Product:	Spiriva® Respimat® (Tiotropium Bromide) Metered-Dose Inhaler
Indication:	Bronchospasm and dyspnea associated with COPD
Applicant:	Boehringer Ingelheim (BI) Pharmaceutical Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Luqi Pei, Ph.D.
Supervisor:	Marcie Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Jessica Lee, Pharm. D.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21-936 are owned by BI or are data for which BI has obtained a written right of reference. Any information or data necessary for approval of NDA 21-936 that BI does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21-936.

OVERALL SUMMARY AND EVALUATION

This review recommends approval of NDA 21-936 from the nonclinical perspective. The 24-MAR-2014 resubmission of the NDA addresses deficiencies identified in the Agency's Complete Response (CR) letter issued to the original application on September 16, 2008. The CR letter did not identify nonclinical deficiencies. The resubmission did not contain significant, new nonclinical data either. Also, the available nonclinical data do not suggest new safety concerns about the proposed use of tiotropium, a currently marketed drug for the same indication. Approval of the Spiriva Respimat NDA is recommended from the nonclinical perspective.

The original NDA 21-936 application was submitted on September 16, 2007. Dr. Luqi Pei completed the nonclinical review of the application on July 29, 2008. That review did not identify any outstanding nonclinical issues. It is unnecessary to generate another review because of the lack of new data. Below is a review of the proposed labeling.

Labeling Review

This labeling review is based on the previous labeling review completed by Dr. Luqi Pei on July 29, 2008, in the same application. Recent changes in labeling format and understanding of the clinical data prompted the current review. Changes in labeling format resulted in the elimination (b) (4) from the currently proposed label. In addition, clinical data showed that Spiriva Respimat (5-mcg tiotropium) and Spiriva HandiHaler (18-mcg tiotropium) produced similar systemic tiotropium exposures in COPD patients. Clinical exposure data prompted a re-evaluation of proposed animal:human exposure ratios in the proposed label.

Nonclinical sections of the proposed labeling are essentially the same as those of the labeling of Spiriva HandiHaler, except for the exposure multiples between animals and humans. This review recommends edits to exposure ratios and labeling format, based on the following discussions.

Exposure Ratios:

The available data does not support tiotropium exposure ratios between animals and humans in nonclinical sections of the proposed labeling. These ratios were derived from Spiriva HandiHaler labeling, according to the submission. To get the exposure multiples for Spiriva Respimat, BI simply multiplied the exposure multiples of the Spiriva HandiHaler by 3.6, the difference in the maximum recommended human daily inhalation dose (MRHDID) of tiotropium between the two products. Specifically, the MRHDID of tiotropium is 18 and 5 mcg for HandiHaler and Respimat, respectively. The original NDA review completed Dr. Luqi Pei on July 29, 2008 used the same approach.

However, the currently available clinical data challenges the appropriateness of the above approach. Clinical data presented in the 14-AUG-2014 Advisory Committee Meeting of the Respimat application indicated that HandiHaler (18 mcg) and Respimat (5 mcg) produced

similar systemic tiotropium AUCs. Data provided by Dr. Yunzhao Ren, clinical pharmacology reviewer, per emails dated August 15, 2014, showed the following: the respective clinical steady state pharmacokinetic parameters of Respimat (5-cmg tiotropium) and HandiHaler (18-mcg tiotropium) were 24.4 and 32.1 ng.h/mL in mean AUC_{0-6} and 12.4 and 15.4 ng/L in C_{max}. The ACU_{0-6} data was used because the plasma drug level at later time points was below the lower limit of detection.[1] The observation that Respimat and HandiHaler produce similar systemic exposures of tiotropium renders it unreasonable to increase the exposure multiples of tiotropium between animals and humans by 3.6-fold. As such, the review commends retaining the exposure ratios of the HandiHaler labeling for the Respimat labeling.

Because both the Spiriva HandiHaler and Respimat contain tiotropium as the only active pharmaceutical ingredient, it is expected that labeling for the nonclinical sections of the two products may be harmonized in the future. Using the exposure multiples from the HandiHaler device now will eliminate the necessity for revising the Respimat labeling.

The approach to derive exposure multiples of tiotropium between animals and humans for the nonclinical sections of Spiriva HandiHaler was discussed extensively during the review of HandiHaler application (Ref.: Nonclinical labeling review completed on December 23, 2003, in NDA 21-395). These discussions resulted in two new Division policies for deriving the dose ratios for labeling reviews at that time:

1) Using the inhaled doses in animals and released doses in humans to derive exposure ratios between animals and humans.
2) Adding the following sentence to explain the exposure multiples: "These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies."

The Division has been following Item 1 in all applications. Item 2, however, has not been used in recent applications. The review recommends removing the statement regarding the inaccuracy of exposure multiples.

Text edits

Edits to the proposed text in Sections 8.1 and 13.1 are recommended so that the product labeling will be compliant with current policies. Also, (b) (4) of the labeling is deleted. Recommended text to the nonclinical sections of the proposed labeling are provided below.

[1] Dr. Ren indicated that the lower systemic tiotropium exposure from the Spiriva HandiHaler was probably the result of a significant portion of the drug being deposited in the mouth and subsequently swallowed following release from the HandiHaler device.

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA RESPIMAT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at approximately 660 and 6 times the recommended human daily inhalation dose (RHDID), respectively (on a mg/m^2 basis at maternal inhalation doses of 1.471 and (b) (4) mg/kg/day in rats and rabbits, respectively). However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at approximately (b) (4) times the RHDID (on a mg/m^2 basis inhalation tiotropium doses of 0.078 mg/kg/day). In rabbits, tiotropium caused an increase in post-implantation loss at approximately 360 times the RHDID (on a mg/m^2 basis at a maternal inhalation dose of 0.4 mg/kg/day). Such effects were not observed at approximately 4 and 80 times the RHDID (on a mg/m^2 basis at inhalation doses of 0.009 and 0.088 mg/kg/day in rats and rabbits, respectively).

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35 and 0.5 times the recommended human daily inhalation dose (RHDID) on a mg/m^2 basis, respectively.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times the RHDID on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m^2 basis).

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/s/

LUQI PEI
08/26/2014

MARCIE L WOOD
08/26/2014

Supervisory Pharmacologist Review

NDA: 21-936 – Spiriva Respimat
FROM: Timothy J. McGovern, Ph. D., Supervisory Pharmacologist
DATE: July 31, 2008

I concur with the recommendation by Dr. Luqi Pei, the pharmacology/toxicology reviewer, that the pharmacology and toxicology of Spiriva® Respimat (tiotropium bromide) have been adequately studied and evaluated and that the drug product is approvable from a nonclinical standpoint (see Dr. Pei's NDA review). Spiriva® Respimat® MDI is a reformulation product of Spiriva® HandiHaler® DPI, an approved and currently marketed product. Both the HandiHaler® and Respimat® use tiotropium bromide as the active moiety. The recommended clinical dose of tiotropium is 18 and 5 µg/day for the HandiHaler® and Respimat® devices, respectively. The nonclinical safety of tiotropium has been established previously in the Spiriva® HandiHaler® application (NDA No. 21-395). There is no new nonclinical data suggesting that the approved 18-µg/day clinical dose is unsafe. The recommended clinical dose of tiotropium for the Respimat® device is only about 28% of the HandiHaler® dose. Therefore, the proposed use of a 5 µg/day dose presents no nonclinical safety issues. The nonclinical data in the HandiHaler® application is sufficient to support the safety and approval of the Respimat® MDI.

Dr. Pei's review details recommended edits to the proposed product labeling which include some modifications of animal to human dosing ratios and of text in sections 8 (b) (4). These recommended edits should be incorporated into the product label prior to approval of the drug product.

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/s/

Timothy McGovern
7/31/2008 12:10:06 PM
PHARMACOLOGIST

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-936**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**November 16, 2007**
PRODUCT:	**Spiriva® Respimat® (Tiotropium Bromide inhalation powder) Metered Dose Inhaler**
INTENDED CLINICAL POPULATION:	**Bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD)**
SPONSOR:	**Boehringer Ingelheim Pharmaceutical Inc.**
DOCUMENTS REVIEWED:	**The original NDA submission - nonclinical**
REVIEW DIVISION:	**Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Timothy McGovern, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Miranda Raggio**

Date of review submission to Division File System (DFS): July 29, 2008

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Approval of Spiriva® Respimat® MDI is recommended from the nonclinical perspective. Spiriva® Respimat® MDI is a reformulation product of Spiriva® HandiHaler® DPI, an approved and currently marketed product. Both HandiHaler® and Respimat® use tiotropium bromide as the active moiety. The recommended clinical dose of tiotropium is 18 and 5 µg/day for the HandiHaler® and Respimat® devices, respectively. The nonclinical safety of tiotropium has been established previously in the Spiriva® HandiHaler® application (NDA No. 21-395). There is no new nonclinical data suggesting that the approved 18-µg/day clinical dose is unsafe. The recommended clinical dose of tiotropium for the Respimat® device is only about 28% of the HandiHaler® dose. Therefore, the proposed use of a 5 µg/day dose presents no nonclinical safety issues. The nonclinical data in the HandiHaler® application is sufficient to support the safety and approval of the Respimat® MDI.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

Edits and revisions of nonclinical sections of the proposed product label are recommended. The text of the nonclinical sections of the proposed label was adopted from that of Spiriva® HandiHaler® DPI, a currently marketed product. The edits are made so that the label will conform to the current Physician's Labeling Rule and to revise animal to human exposure ratios due to the differences in the recommended daily dose. Revisions are primarily limited to the proposed dose ratios between animals and humans. The revisions are made to accurately reflect the clinical use conditions, for the recommended clinical daily tiotropium dose in HandiHaler® is 3.6 times that in the Respimat®. Additional information on edits and revisions can be found in the Labeling Review section (page 12). The sponsor's proposed labeling regarding nonclinical sections is presented below. Suggested inserts are presented as underlines and suggested deletions are presented as strikeouts.

(b) (4)

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings
Not applicable to this review because no data was submitted. The active ingredient is an approved and currently marketed drug. All pivotal nonclinical data in support of the approval of tiotropium were submitted and reviewed previously under NDA 21-395 (approved in January 2004). The labeling of Spiriva HandiHaler® states that

(b) (4)

B. Pharmacologic activity
Not applicable to this review because no data was submitted.

C. Nonclinical safety issues relevant to clinical use
None.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

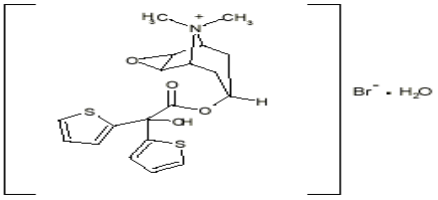
2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-936
Review number: 1
Sequence number/date/type of submission: 000/ 18-NOV-2007/ Original NDA
Information to sponsor: Yes (x), No ( )
Sponsor and/or agent: Boehringer Ingelheim Pharmaceuticals, Inc.
Manufacturer for drug substance: The same as above

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: July 30, 2008

Drug:

Trade Name: Spiriva® Respimat
Generic Name: Tiotropium bromide inhalation dry powder
Code Name: Ba 679 BR
Chemical Name: (1α, 2β, 4β, 5α, 7β)-[(hydroxydi-2-thienylacetyl)-9,9-dimethyl-3-oxa-9-azoniatrcyclo[3.3.1.$0^{2,4}$]nonane bromide monohydrate
CAS Registry Number: N/A
Molecular Formula/Weight: $C_{19}H_{22}NO_4S_2Br.H_2O$/ 490.3
Structure:



Relevant INDs/NDAs/DMFs: NDA 21-395; INDs 46,687 and 65,127

Drug Class: Muscarinic cholinergic receptor antagonist

Intended clinical population: Bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD); the maximum recommended daily dose is 5 µg/day

Clinical formulation: Aqueous inhalation aerosol solution delivered by a metered dose inhaler – Spiriva® Respimat®. The solution contains (b) (4) benzalkonium chloride and (b) (4) EDTA sodium as preservatives. Each actuation delivers 2.5 µg tiotropoium

Route of Administration: Oral inhalation

Disclaimer: *Tabular and graphical information are constructed by the reviewer unless cited otherwise.*

Studies reviewed within this submission:

Effects of tiotropium bromide on HERG-mediated potassium channel current in HEK923 cells and on action potential configuration in isolated of guinea pig papillary muscles, Doc. No. U01-1720, Report/Study No. GP2001/254/275/PH2, Section 4.2.1.3 Safety Pharmacology.

Studies not reviewed within this submission: None.

Background:

Spiriva® Respimat®, the applicant's product, is a reformulation product of Spiriva® HandiHaler®, an approved and currently marketed product in the US. Spiriva® HandiHaler® also incorporates a new inhalation device. Both products contain tiotropium bromide as the active ingredient. They will also have the same clinical indications: the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.

Respimat® and HandiHaler®, however, will have significant differences. These differences are in the device, formulations and clinical tiotropium doses. Regarding the formulation, HandiHaler® is a dry powder inhaler containing lactose as the excipient. Respimat® is an aqueous aerosol containing EDTA (b) (4) and benzylconium chloride (b) (4) as the excipient. Regarding the dose, the recommended daily clinical dose of tiotropium will be 5 and 18 μg for Respimat® and HandiHaler®, respectively. The daily dose will be delivered by one (HandiHaler®) or two (Respimat®) actuations.

Spiriva® HandiHaler® was approved in January 2004 (NDA 21-395). All pivotal nonclinical safety data in characterizing the toxicity profile of and in support of the marketing of tiotropium applications were submitted and reviewed in the Spiriva® HandiHaler® application.

Spiriva® Respimat® was developed under IND 65,127 (IND filing date of July 30, 2002). A Pre-NDA meeting was held on April 25, 2005. The meeting minutes states that no additional toxicity studies of tiotropium were needed for the Spiriva® Respimat® application. The minutes also state that the NDA submission should address issues of degradants, impurities, leachables and extractables.

Filed on November 18, 2007, the original submission contained no new pivotal nonclinical data. The application refers to the nonclinical data submitted for NDA 21-395. The submission did contain *in vitro* safety pharmacology studies evaluating effects of tiotropium on HERG-mediated potassium channel current in HEK923 cells and on action potential of guinea pig papillary muscles that had not been previously submitted or reviewed.

The application submitted several versions of the proposed labeling. The most recent version was submitted on June 20, 2008. The nonclinical sections of these versions including those in the original and 20-JUN-2008 submissions, however, were identical. This document reviews the label based on the 20-JUN-2008 submission.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief Summary

No significant new data was submitted. The following summary was based on a pharmacology and toxicology review completed by Dr. Luqi Pei on September 17, 2002 in NDA 21-395.

Tiotropium is a long-acting muscarinic cholinergic receptor antagonist. It binds reversibly to muscarinic cholinergic receptors located in the airways, blocks the bronchoconstriction of acetylcholine, and results in bronchodilation. Tiotropium has a high affinity to m_3, m_4 and m_5 receptors (Kd = 9 pM) and a relatively low affinity to m_2 and m_1 receptors (Kd = 32 – 151 pM). The median effective inhalation dose (ED_{50}) of tiotropium against acetylcholine-induced bronchoconstriction is approximately one μg/kg in guinea pigs, rabbits and dogs. The to-be-marketed clinical dose of tiotropium in COPD patients is 18 μg once a day (*i.e.*, 0.36 μg/kg/day).

The secondary pharmacological effect of tiotropium may include tachycardia and inhibition of salivation, and lacrimation and bowl movement. The inhibition of salivation, probably the earliest indicator of tiotropium side effects, occurs at five times the bronchodilatory effect in guinea pigs.

The submission contains a safety pharmacology study that reported that tiotropium bromide had no effect on HERG-mediated potassium channel current in HEK923 cells. Nor did it affect action potential configuration in isolated of guinea pig papillary muscles in vitro. However, a pharmacology and toxicology review completed by Dr. Luqi Pei on September 17, 2002 in NDA 21-395 states that tiotropium at therapeutic plasma concentrations may increase heart rate and inhibit salivation and gastrointestinal motility. These effects appear to be secondary pharmacological activity of typical muscarinic antagonists.

2.6.2.2 Primary pharmacodynamics

No new data were submitted.

2.6.2.3 Secondary pharmacodynamics

No new data were submitted.

2.6.2.4 Safety Pharmacology

No significant new data was submitted.

Cardiovascular effects: Report/Study No. GP2001/254/275/PH2, Document No. U01-1720 is a safety pharmacology study that evaluates effects of tiotropium bromide on HERG-mediated potassium channel current in HEK923 cells and on action potential configuration in isolated of guinea pig papillary muscles in vitro. The tiotropium concentrations were 0.1 – 100 μM in

HEK923 cells and 0.1 – 50 μM in papillary muscle cells, respectively. The effect on potassium channel current was determined using a voltage clamp technique. The effect on action potential was evaluated by APD10, APD30 and APD90 (time needed to 10%, 30% and 90% membrane repolarization) and other parameters. The study did not reveal any effect of tiotropium on these testing systems.

2.6.2.5 Pharmacodynamic drug interactions

No new data was submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No data was submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

No data was submitted. According to the pharmacology and toxicology review completed by Dr. Luqi Pei on September 17, 2002 in NDA 21-395, inhaled tiotropium was readily bioavailable in animals. Tiotropium had a large volume of distribution and a long terminal half-life. Metabolism of tiotropium occurred in the liver. Glucuronide conjugates were the primary metabolites in the liver. Non-enzymatic hydrolysis occurred in the plasma. The drug was primary excreted in the urine in unchanged form. Drug accumulation occurred in the rat and a steady state was reached within three months.

2.6.4.2 Methods of Analysis

No new data was submitted.

2.6.4.3 Absorption

No new data was submitted.

2.6.4.4 Distribution

No new data was submitted.

2.6.4.5 Metabolism

No new data was submitted.

2.6.4.6 Excretion

No new data was submitted.

2.6.4.7 Pharmacokinetic drug interactions

No new data was submitted.

2.6.4.8 Other Pharmacokinetic Studies

No new data was submitted.

2.6.4.9 Discussion and Conclusions

See the summary above.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

No data was submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

The current application contained no toxicology data about the toxicity profile of tiotropium. The application refers to the data submitted for NDA 21-935. The pharmacological and toxicological profile of tiotropium has been characterized previously during the development of the currently marketed Spiriva® HandiHaler® dry powder inhaler (NDA 21-395). The approved label of the Spiriva® HandiHaler® states (b) (4) These effects have been clearly described in the approved label for Spiriva HandiHaler . The lack of any new toxicology data of tiotropium in the current application precludes any modifications nonclinical findings described in the approved label. Nonclinical sections of the approved Spiriva® HandiHaler® labeling are as follows:

> "**Carcinogenesis, Mutagenesis, Impairment of Fertility:** No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to 25, 35, and 0.5 times the Recommended Human Daily Dose (RHDD) on a mg/m^2 basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDD on a mg/m^2 basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDD on a mg/m^2 basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDD on a mg/m^2 basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Pregnancy Category C: No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up [redacted] to approximately 660 and 6 times the recommended human daily dose (RHDD) on a mg/m^2 basis. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of [redacted] (approximately 35 times the RHDD on a mg/m^2 basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of [redacted] (approximately 360 times the RHDD on a mg/m^2 basis). Such effects were not observed at inhalation doses [redacted] in rats and rabbits, [redacted] correspond to approximately 4 and 80 times the RHDD on a mg/m respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies."

2.6.6.2 Single-dose toxicity

No data was submitted.

2.6.6.3 Repeat-dose toxicity

No data was submitted.

2.6.6.4 Genetic toxicity

No data was submitted.

2.6.6.5 Carcinogenicity

No data was submitted.

2.6.6.6 Reproductive and Developmental Toxicology:

No data was submitted.

2.6.6.7 Local tolerance

No information was submitted.

2.6.6.8 Special toxicology studies

No information was submitted.

2.6.6.9 Discussion and Conclusions

No discussion is needed because the submission did not contain any toxicity studies.

2.6.6.10 Tables and Figures

No information was submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

No information was submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The available data support the approval of the Spiriva® Respimat® application (NDA 21-936) from the nonclinical perspective. Spiriva® Respimat® is a reformulation product of Spiriva® HandiHaler® that is an approved and currently marketed product in the United States. The new product also incorporates a new inhalation device. With tiotropium bromide as the active ingredient, both HandiHaler® and Respimat® will be indicated for the same diseases. The two products have differences in formulations and recommended daily doses; these differences do not, however, have any significant impact on the nonclinical safety evaluations of inhaled tiotropium. The reason is that the recommended dose for the Respimat product will be lower than the approved HandiHaler (5 μg versus 18 μg). The Respimat® application contained no significant nonclinical data, for all nonclinical data characterizing the toxicity profile of tiotropium have been previously submitted and reviewed by the Agency under the HandiHaler® application. The Respimat® application satisfactorily addressed all the nonclinical safety issues. Previous communications with the sponsor agreed that no additional nonclinical studies would be required to support the approval of the drug product. Approval of the application is recommended, pending labeling revisions indicated in the labeling review section.

Nonclinical safety support of the application relies on the Agency's previous finding that there was adequate data to support inhaled tiotropium at a higher dose. Approved in 2004, the Spiriva® HandiHaler® (NDA 21-395) is a dry powder inhaler indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Spiriva® will be indicated for the same diseases.

Respimat® and HandiHaler® will differ in formulation and recommended daily dose of tiotropium. Regarding the formulation, HandiHaler® is a dry powder inhaler containing lactose as the excipient. Respimat® is a metered dose inhaler with aqueous aerosols containing EDTA (b) (4) and benzalkonium chloride (b) (4) as excipients. The maximum recommended daily dose of tiotropium is 5 and 18 μg/patient for the Respimat® and

HandiHaler®, respectively. Boehringer Ingelheim Pharmaceuticals is the owner of tiotropium nonclinical data and sponsor of both Spiriva® Respimat® and HandiHaler®. Because the recommended clinical daily tiotropium dose in Respimat® is only 28% of the dose approved for the HandiHaler® product, the available nonclinical data in NDA 21-395 is adequate to support the safety of the current application.

There is no nonclinical safety concern about the excipients in the Respimat® device. Respimat® emits aqueous aerosols containing EDTA (b) (4) and benzalkonium chloride (b) (4) as excipients. These excipients at similar concentrations are present in other currently marketed products and their safety is considered to have been established.

The application has adequately addressed issues of degradants, impurities, leachables and extractables. Dr. Luqi Pei's Chemistry Consultation Review completed on May 6, 2008. in the application evaluates the safety of potential degradants, impurities, leachables and extractables. The review finds no safety concerns about the potential extractables and leachables.

Excipients

There is no safety concern about excipients present in Spiriva® Respimat®. Spiriva® Respimat® contains (b) (4) benzalkonium chloride and (b) (4) edetate disodium (EDTA). Both are commonly used excipients in inhalation aerosol products. Alupent® inhalation solution (metaproterenol sulfate, NDA 17-659) is an example. The concentration of each compound is equal to the lowest concentration in the marketed products (b) (4). Due to the small volume of administration, (b) (4) expected daily exposure of each compound from Spiriva® Respimat® is a fraction of exposure from other marketed products. The safety of the excipients in Spiriva® Respimat® is considered established.

Unresolved toxicology issues (if any): None.

Recommendations: Approval is recommended from the nonclinical perspective.

Suggested labeling:

The review recommends edits of and revisions to nonclinical sections of the proposed product labeling for Spiriva® Respimat®. The edits are necessary because of the creation of new headings required by the current Physician's Labeling Rule. The revisions are generally limited the tiotropium dose ratios between animals and humans.

Format of the proposed label was generally in compliance with the current Physician's Labeling Rule. The content of the nonclinical sections of the label was adopted from the label of Spiriva® HandiHaler® that is currently on the market due to the lack of nonclinical data in the current application. All nonclinical studies pertinent to the labeling of tiotropium, the active ingredient in both the HandiHaler® and Respimat® devices, were submitted and reviewed previously under the application (NDA 21-395). These studies included studies of genetic toxicity, carcinogenicity, reproductive and developmental toxicity. Please see Section 2.6.6.1 (Overall Toxicology Summary, page 8) for the HandiHaler® labeling.

In comparison with HandiHaler® label, the Respimat® label created new headings and subheadings. The new headings include Use in Specific Populations (Section 8) and

Nonclinical Toxicology (Section 13)]. (b) (4) The subsection of Carcinogenesis, Mutagenesis, and Impairment of Fertility was given a number (Section 13.1) and placed under Section 13. The new headings and subheadings made it necessary to rearrange the animal findings. Edits are recommended to the Pregnancy section to conform to recent recommendations from CDER's SEALD team. These edits are meant to focus the text on the primary reproductive findings and the animal to human exposure ratios at which they occur to present the most relevant information to the reader.

Modification of the proposed dose ratios between animals and humans are made to reflect more accurately these multiples. The recommended daily dose of tiotropium is 5 and 18 µg/day for Respimat® and HandiHaler® (18 µg/day), respectively. The decrease in tiotropium dose in Respimat® results in a 3.6-fold increase in dose multiples (ratios) between animals and humans, when compared to HandiHaler® for a given animal dose. Using the carcinogenicity data as an example, the ratio will be 25 and 90 for HandiHaler® and Respimat®, respectively.

The sponsor proposed to use the same dose ratios for both the HandiHaler® and Respimat® devices. The proposal seems reasonable because such ratios would reflect the worst case scenario for both drug products. It also makes it possible and acceptable for the two products to use a common label for the nonclinical sections. However, it was decided that each product label should have accurate information about the intended use. The review, therefore, revises the proposed dose ratios between animals and humans.

The new ratios between animals and humans were calculated on a mg/m^2 basis. The ratios were obtained by dividing estimated exposures, on a mg/m^2 basis, in animals by that in humans. The mg/m^2 dose in a given species were calculated by multiplying the nominal dose (i.e., in mg/kg/day) by a conversion factor for that species. The nominal doses in animals were extracted from the approved labeling of the HandiHaler®. The human exposure was 0.0037 mg/m^2 [0.005 mg/day ÷ 50 (kg) x 37 (km) = 0.0037). Appendix 1 (page 17) listed the nominal dose, mg/m^2 dose, and dose ratios used to generate the new dose ratios. Furthermore, the newly suggested ratios followed the current rounding rules.

The sponsor's proposed labeling regarding nonclinical sections is presented below. Suggested inserts are presented as underlines and suggested deletions are presented as strikeouts.

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Luqi Pei, Ph.D.
Senior Pharmacologist/Toxicologist

APPENDIX/ATTACHMENTS

Appendix A: Exposure Ratio Tables for the Labeling Review

Drug: **Spiriva Respimat**

	age	mg/dose	# daily doses	mg/day	kg	mg/kg	factor	mcg/m²
Pediatric				0	3	0.00	25	0.00
Adult	>12	0.005	1	0.005	50	0.00	37	0.0037

	route	mg/kg/d	conv. factor	mg/m²	Dose Ratio Adults	Dose Ratio Children	Rounded Dose Ratio Adults	Rounded Dose Ratio Children
Carcinogenicity:								
rat	IH	0.059	6	0.354	95.7	---	95	---
mouse	IH	0.145	3	0.435	117.6	---	120	---
mouse	IH	0.002	3	0.006	1.6	---	2	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
Reproduction and Fertility:								
rat	IH	0.078	6	0.468	126.5	N/A	130	N/A
rat	IH	0.009	6	0.054	14.6	N/A	15	N/A
rat	IH	1.689	6	10.13	2738.9	N/A	2700	N/A
extra			---	---	---	N/A	---	N/A
Teratogenicity:								
rat	IH	1.471	6	8.826	2385.4	N/A	2400	N/A
rabbit	IH	0.007	12	0.084	22.7	N/A	25	N/A
rat	IH	0.078	6	0.468	126.5	N/A	130	N/A
rabbit	IH	0.4	12	4.8	1297.3	N/A	1300	N/A
rat	IH	10.5	6	63	17027.0	N/A	17000	N/A
Overdosage:								
mouse	IH	32.4	3	97.2	26270.3	---	26000	---
rat	IH	267.7	6	1606	434108.1	---	434000	---
dog	IH	0.6	20	12	3243.2	---	3200	---
extra			---	---	---	---	---	---
Other:	teratogenicity							
rat	IH	0.009	6	0.054	14.6	---	15	---
rabbit	IH	0.088	12	1.056	285.4	---	290	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---
extra			---	---	---	---	---	---

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/s/

Luqi Pei
7/29/2008 02:16:36 PM
PHARMACOLOGIST

Timothy McGovern
7/29/2008 02:40:37 PM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY AND TOXICOLOGY REVIEW

CHEMISTRY CONSULT

Safety Evaluations of Impurities, Extractables and Leachables, and Excipients

NDA No.:	21-936
Drug Name:	Spiriva® Respimat®
Sponsor:	Boehringer Ingelheim Pharmaceuticals
Submission date:	November 16, 2007
Consultation request date:	February 5 and March 27, 2008
Reviewer:	Luqi Pei, Ph.D., Senior Pharmacologist
Review completion date:	May 6, 2008

This review finds no safety concerns about the proposed specifications for tiotropium impurities in the drug substance and in Spiriva® Respimat® inhalation aerosol from the nonclinical perspective. Neither does it identify a concern about the proposed specifications for leachables, particulate matters, and the use of benzalkonium chloride and EDTA as excipients. These conclusions are based on following: 1) impurity specifications in the drug substance are identical to what the Agency had allowed previously for Spiriva Handihaler; 2) estimated maximum daily exposure of each impurity in a patient trough use of the drug product is smaller than its acceptable daily intake qualified previously; 3) estimated daily exposures of each leachable and/or extractable are below the Division's current safety qualification threshold; 4) estimated daily exposures of particulate matter are minimal, and 5) concentrations of EDTA and benzalkonium chloride are within the range of the respective concentrations in currently marketed inhalation products.

The review was generated in response to two consultation requests filed by Drs. Prasad Peri and Alan Schroeder on February 5, and March 27, 2008, respectively. Dr. Prasad Peri, Chemistry Team Leader, requested safety evaluations of the following: the proposed levels of impurities in the drug product, the proposed levels of extractables, leachables and particulate matters in the drug product, benzalkonium chloride and disodium edentate as excipients in the drug product, and the results of USP <87> and <88> testes for the device. Dr. Schroeder, Chemistry Reviewer, refined the leachable specifications. The safety evaluations are presented in the following order: impurities, leachables and extractable, particulate matters, benzalkonium chloride and EDTA sodium, and USP tests.

Drug Substance and Product Impurities

There are no nonclinical safety concerns about the proposed specifications for tiotropium impurities or degradation products in drug substance and drug products. The impurity specifications in the drug substance are acceptable because impurity concentrations are not

only below the ICH qualification threshold but also identical to these considered acceptable previously. The specifications in the drug product are acceptable because the amount of estimated daily intake for each impurity in a patient is smaller than what was considered qualified previously.

Impurities in Drug Substance

A total of seven impurities in the drug substance of tiotropium were reported. (b) (4) (b) (4) (b) (4) These impurities had been identified in the drug substance previously in the original tiotropium application (NDA 21-395). The proposed specifications for each of these impurities (b) (4) in the current application are identical to the acceptable criteria listed in Item 3.c of the NDA approvable letter dated December 20, 2002 in NDA 21-395. Also, these specifications are below the qualification threshold of 0.15% or 1.0 mg/day for drugs with the maximum daily dose of less than 2 grams/patient defined in the ICH guidance: ICH-Q3A: Impurities in New Drug Substances. Furthermore, none of them have structural alerts for genotoxicity or testing positive in genetic testing assays.[1] There is no new information warranting the criteria set previously for the drug substance. Overall, the proposed specifications for impurities are considered safe and acceptable.

Impurities in Drug Product

A total of 4 tiotropium impurities and degradation products were reported in the drug product. (b) (4) proposed specifications were (b) (4) respectively. Each of the above compounds has been reported previously in the Spiriva HandiHaler® application (NDA 21-395). Dr. Luqi Pei evaluated the nonclinical safety of these compounds in Chemistry Consult Reviews completed on August 28, 2002, and January 25, 2006 in NDA 21-395. The 25-JAN-2006 review finds that the nonclinical data available then support the specifications of (b) (4) in Spiriva® HandiHaler®, an approved and currently marketed product.

This review conducts its nonclinical safety evaluations of tiotropium impurities in the Spiriva® Respimat® MDI by comparing the estimated daily intake (EDI) of each impurity to its acceptable daily intake (ADI) set for the Spiriva® HandiHaler® dry powder inhaler (DPI). An EDI is calculated by multiplying the maximum recommended human daily dose (MRHDD) of tiotropium by the concentration (i.e., the proposed specification) of the impurity of interest. The MRHDD of tiotropium is 18 and 5 µg/day for Spiriva® HandiHaler® DPI and Spiriva® Respimat® MDI, respectively. Because the MRHDD of tiotropium in the current application (5 µg) is less than one-third of the currently approved

[1] Source: Chemistry Consult Review completed by Dr. Luqi Pei completed on August 2, 2008 in NDA 21-395.

[2] (b) (4) in Dr. Prasad Peri's request. Dr. Alan Schroeder confirmed via an email message dated April 22, 2008 that (b) (4) were the same compound.

dose, the review considers the EDI (or specification) of an impurity acceptable if the proposed specification is equal to or below the acceptable one set for the Spiriva® HandiHaler® DPI. Consequently, the review finds the proposed specifications for (b) (4) (b) (4) of no safety concern because they are below the acceptable specifications for Spiriva® HandiHaler® DPI.

The review also finds no safety concern for the proposed specification for (b) (4). The conclusion is based on the finding that the Spiriva® Respimat® MDI will have a lower EDI of (b) (4) than the HandiHaler® DPI, although the former will have a higher specification for (b) (4) than the latter (b) (4). The EDI of (b) (4) is approximately (b) (4) for Spiriva Respimat® MDI and Spiriva® HandiHaler® DPI, respectively.

The review finds that the proposed specification for (b) (4) is of no concern because it is significantly below the qualification threshold of 1.0% for this class of drug products (i.e., the total daily dose equal to or smaller than 10 mg).

Leachables and Extractables

Dr. Prasad Peri's request contains lists for potential extractables in the drug product while Dr. Schroeder request provided a list for leachables (Appendix A). Neither list identified (b) (4) as extractables or leachables. Safety evaluations of this review are based on the leachable specifications because they mimic the clinical situations.

Table 1 Leachables and Their Estimated Daily Intakes

Leachable	Max. Observed Levels (ug/ml)	Total Daily Intake (ng/day) [a]
(b) (4)		

a. As indicated in Dr. Alan Schroeder's request (Appendix). The TDI is calculated by multiplying the maximum observed level by the target delivered volume ((b) (4) per dose; one dose per day).

b. The number with sign "<" in the column of Maximum Observed Level indicates the level of quantitation (low) for compounds that were not detected during the assay. The sum of all leachables is an only exception. It stands for" "not more than".

Table 1 (Previous page) lists the leachables and their estimated daily intakes. Most leachables are compounds commonly seen in inhalation devices: (b) (4) The total daily intake is generally smaller than (b) (4) except for (b) (4) that may reach as high as (b) (4). These levels are smaller then the Division's current respective qualification thresholds of 0.15 and 5 µg/day/patient for genotoxic and non-genotoxic compounds, respectively, that are based on recommendations made by a Leachable and Extractables Working Group of the Product Quality Research Institute. The proposed specifications for leachables and extractables in Spiriva® Respimat® are considered acceptable from the nonclinical perspective.

Particulates

There are no safety concerns about the proposed specifications of particulate matter in the Spiriva® Respimat® MDI. Dr. Prasad Peri's Chemistry Consult Request states that the proposed specifications for particulate matter are (b) (4) for particles with diameters of (b) (4) respectively. The estimated daily exposures of the particulates were (b) (4) for particle diameters (b) (4) respectively (Table 2). The daily exposure to the fine particles (b) (4) is negligible (b) (4) and is well below the EPA recommended limit of 300 µg/day [i.e., for an adult breathing 20 m^3- air with 15-µg/m^3 particulates ($P_{2.5}$) per day]. Particles with large diameter are only a few. Also, these large particles are not expected to reach the pulmonary region which is of more safety concern. Overall, the proposed specifications for particulate matters are acceptable.

Table 2 Estimated Daily Intakes of Particulate Matters in Spiriva Repsimat

(b) (4)

EDTA and Benzalkonium Chloride

The presence of EDTA sodium and benzalkonium chloride (b) (4) as excipients in Spiriva® Respimat® inhalation aerosols is of no safety concern from the nonclinical perspective. Dr. Luqi Pei evaluated previously the safety of EDTA sodium and benzalkonium chloride in inhalation drug products. The evaluation was documented in a memorandum to Dr. Robert Osterberg, the Chair of the Inactive Ingredient Committee then, completed on March 24, 1999. The memorandum is entitled "Safety Evaluation of EDTA and Benzalkonium Chloride in Inhalation Drug Products." The memorandum concluded that EDTA at concentrations of (b) (4) and benzalkonium chloride at concentrations of (b) (4) in inhalation drug products safe whether the compounds presented alone or in combination. The proposed concentration for each excipient is at the lower end of the safe range. The concentration is considered safe and acceptable.

USP tests <87> and <88>

It is not necessary to review reports of USP tests <87> and <88>. The reason is that the Agency reviewed them previously in the Spiriva® HandiHaler® dry powder inhaler application. Dr. Brian Roger's Chemistry Review #1 in NDA 21-395 had the following description about the tests:

> "Report LPT 11862/98 (p. 295) shows the results of the USP <87> testing (Mouse fibroblasts, ATCC, CCL1, NCTC clone L 929) were acceptable. No cytotoxicity was observed for the extract obtained from the mouthpiece. The control produced severe toxicity.
>
> Report LPT 11859/98 (p. 333) shows the results of the USP <88> testing from four solvents: 0.9% NaCl solution; 1:20 water:alcohol in 0.9% NaCl; Polyethylene glycol 400; and Sesame oil. None of the extracts after 72 hours (and intervening periods) showed any systemic intolerance reactions. LPT 11860/98 shows a similar result in subcutaneous testing in rabbits."

Conclusion

The proposed specifications for tiotropium impurities in drug substance and the Spiriva® Respimat® MDI and specifications for leachables, extractables, particulate matters, benzalkonium chloride and EDTA in the drug product are of no significant safety concerns under the intended use.

Luqi Pei, Ph.D.,
Senior Pharmacologist/Toxicologist

Appendix A: Leachable List Provided by Dr. Alan Schroeder on 28-MAR-08

(b) (4)

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/s/

Luqi Pei
5/6/2008 08:05:29 AM
PHARMACOLOGIST

Timothy McGovern
5/6/2008 08:33:01 AM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

NDA 21-Day Pharmacology Fileability Check List

Reviewer: Luqi Pei, Ph.D.

NDA No: 21-936
Drug Name: Spiriva® Respimat®
Date of submission: November 16, 2007
Date of 45-day file-ability meeting: December 19, 2007
Information to the Sponsor: None.
Filing date: January 15, 2008
Date of check list: January 23, 2008

(1) On its face, is the pharmacology/toxicology section of the NDA organized in a manner to allow substantive review? Yes.

(2) On its face, is the pharmacology/toxicology section of the NDA legible for review? Yes.

(3) Are final reports of all required and requested preclinical studies submitted in this NDA? Final reports of all toxicology study reports are submitted. Yes.

	Yes	No	NA
Pharmacology	( )	( )	(x)
ADME	( )	( )	(x)
Toxicology (duration, route of administration and species specified)			
acute	( )	( )	(x)
subchronic and chronic studies	( )	( )	( )
reproductive studies	( )	( )	(x)
carcinogenicity studies	( )	( )	(x)
mutagenicity studies	( )	( )	(x)
special studies	( )	( )	(x)
others *	( )	( )	(x)

* The application is a reformation of the current marketed product, Spiriva® Handihaler. All relevant toxicity study reports have been submitted and reviewed previously in NDA 21-395.

(4) If the formulation to be marketed is different from the formulation used in the toxicology studies, are repeating or bridging the studies necessary? No.

If no, state why not: The to-be-marketed formulation and the formulation used in toxicity studies are similar. Bridging toxicity studies, therefore, is not necessary. Also, the Division agreed with the nonclinical program in a pre-NDA meeting held on April 25, 2005.

If yes, has the applicant made an appropriate effort to repeat the studies using the 'to be marketed' product, to bridge the studies or to explain why such repetition or bridging should not be required?

(5) Are the proposed preclinical labeling sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and over-dosage) appropriate (including human dose multiples expressed in either mg/m^2 or comparative systemic exposure levels) and in accordance with 201.57?

Yes. The label does follow the new product labeling recommendations (PLR). Dose ratios between animals and humans in preclinical sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and over-dosage) are appropriate as they are expressed in mg/m^2. The text of these nonclinical sections, including the dose ratios between animals and humans, is identical to what has been approved for Spiriva®. The recommended daily dose of tiotropium for Spiriva® Respimat® is only 28% of that for Spiriva® Handihaler. The use of the same ratios for the Handihaler and Respimat results in overestimate the risk. Such a practice is of no safety concern.

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? N/A.

(7) On its face, does the route of administration used in the pivotal toxicity studies appear to be the same as the intended clinical route? Yes.

If not, has the applicant submitted a rationale to justify the alternative route? Yes/No

(8) Has the applicant submitted a statement(s) that all of the toxicity studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? N/A.

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? No.

(10) Are there any outstanding preclinical issues? No.

If yes, identify those below

(11) From a preclinical perspective, is this NDA fileable? Yes.

If no, state below why it is not.

If yes, should any additional information/data be requested? No. The Division and the Sponsor held a pre-NDA meeting on April 20, 2005. The nonclinical section of the minute addresses issues of degradants, impurities, leachables and extractables in the NDA submission. No other nonclinical issues were identified. Issues of degradants, impurities, leachables and extractables appear to be addressed in the CMC section of the submission in the NDA submission.

If yes, identify those below.

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/s/

Luqi Pei
1/23/2008 12:58:25 PM
PHARMACOLOGIST

Timothy McGovern
1/23/2008 01:17:56 PM
PHARMACOLOGIST
I concur.