rapidly reaches steady state, they felt that a study period of 3 weeks would be sufficient to support a claim for —— To assess the durability of effect, FDA stated that 6 weeks would be needed to support an efficacy claim.

9. BI did not feel that Holter monitoring would be necessary as all changes on ECG and rhythm strip monitoring in their 4 week multiple dose study (205.108) were, for the most part, transient and persisted only in the placebo group. FDA emphasized that there is concern about potential cardiotoxicity with an anticholinergic NME that has a prolonged half-life. It was strongly suggested that BI perform holter monitoring at baseline and for a full 24 hours post dose. FDA suggested using one of the centers where the a.m./p.m. studies are being conducted to better assess cardiac effects occuring during oxygen desaturations with sleep in patients receiving p.m. dosing.

10. BI agreed to this proposal. A definition will be added to the protocol.

11. Clarifications will be made by BI as requested.

12. FDA emphasized the need for BI to conduct *in vivo* testing of the to-be-marked device (Handihaler) in a small group of patients to determine what peak flows can be generated through the device. FDA also suggested using COPD patients with poorer pulmonary function tests to determine their ability to receive an adequate quantity of the drug. BI plans to conduct *in vitro* testing at 28L/min, and agreed to the merits of testing flow rates *in vivo* with at least a small number of COPD patients with poor pulmonary function.

Statistics

Refer to comments #13-19 on the November 26, 1996 fax.

13. BI stated that the purpose of the interim analyses is not to determine if the study should stop but to determine if results are adequate for submission of an NDA.

14. According to BI, the primary time period of analysis is 13 weeks. This will be specified in the protocol.

15 thru 19. The Agency and BI agreed that, potentially, dropouts and the use of concomitant medication may create problems with the analysis and interpretation of study results. Due to time constraints, the details of the analyses could not be discussed in this meeting. BI plans to submit a statistical plan prior to the unblinding of the studies that will address these concerns.

Conclusions

In general, many of the points discussed were agreeable to both FDA and BI.

The following key points were emphasized at the conclusion of the meeting.

1. BI's ranges for the emitted dose are too wide. They should be in the same range as Combivent (a recently approved pulmonary drug).

2. The mass balance issue in the particle size distribution profile at release and stability needs to be addressed.

3. The sponsor will need to validate the [redacted] instruments *a priori* and describe in advance clinically meaningful changes.

4. The study to determine [redacted] will need to be for 6 weeks.

5. Holter ECG monitoring will need to be conducted for 24 hours post dosing to examine potential arrhythmias, as well as heart rate effects.

6. In-vivo flow rates need to be generated through the Handihaler device using at least a small number of COPD patients with poor pulmonary function.

Ms. Schumaker informed the sponsor that the Division is in the process of making a guidance for the Pre-NDA meeting that is similar to the End-of-Phase 2 guidance. Background packages will be needed several weeks in advance of the meeting. A team meeting approach will be used with all disciplines present rather than meeting with individual disciplines separately.

LST

- ATTACHMENTS A, B, & C

cc:
IND 46,687
HFD-570/Division Files
HFD-570/Honig/12-20-96
HFD-570/Trontell/12-12-96
HFD-570/Poochikian/12-16-96
HFD-570/Ng/12-12-96
HFD-570/Rogers/12-12-96
HFD-570/Sun/12-12-96
HFD-570/Tripathi/12-12-96
HFD-570/Wilson/12-17-96

HFD-570/Bono/12-13-96
HFD-570/Schumaker/12-19-96
HFD-570/Kuzmik/12-06-96
HFD-570/Conner/12-12-96
HFD-570/Gillespie/12-12-96

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END-OF-PHASE 2 MEETING MINUTES

7 Page(s) Withheld

Memorandum of Telephone Facsimile Correspondence

Date: January 14, 2004

To: Eileen Wyka
Director, Technical Drug Regulatory Affairs

From: Alan Schroeder, Ph.D.

Through: Anthony M. Zeccola

Subject: CMC Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

This pertains to specifications for [redacted] which are part of the HandiHaler specifications that were first provided in your December 4, 2003, amendment and clarified in your January 5, 2004, amendment. Modify the functional acceptance criteria for [redacted] to defect class 1, since these are considered to be critical parameters for patient use of the device. Reassess your acceptance criteria for [redacted] in terms of the number of failures allowed, considering that this is an inhalation drug product. If failure of the [redacted] criterion would prevent the patient from getting a proper dose, then also modify this acceptance criterion to defect class 1.

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/s/

Anthony Zeccola
1/14/04 01:37:23 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: December 23, 2003

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Eugene Sullivan, M.D.

Through: Anthony M. Zeccola

Subject: Clinical Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

The application states that the Dutch authorities have requested that the Summary of Product Characteristics document be revised to expand the statements regarding allergic reactions. You have proposed to add reference to post-marketing events of urticaria and pruritis in the US product label. Provide further details and explanation regarding the data that generated these concerns.

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/s/

Anthony Zeccola
12/23/03 03:26:56 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: December 23, 2003

To: Eileen Wyka
Director, Technical Drug Regulatory Affairs

From: Alan Schroeder, Ph.D.

Through: Anthony M. Zeccola

Subject: CMC Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

This pertains to your commitment to [redacted] refer to responses 16a(1) and 16a(2) in your amendment dated December 4, 2003). Provide an agreement to discuss with the Agency, details of your future proposal for [redacted]

APPEARS THIS WAY
ON ORIGINAL

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/s/

Anthony Zeccola
12/23/03 03:13:05 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: December 23, 2003

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Anthony M. Zeccola

Subject: Preliminary Labeling Comments (Clinical and CMC) – NDA 21-395

Total Pages: 6 including this page and electronic signature page

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

As discussed during our telephone conversation earlier today, the following are labeling comments which have been provided from our Clinical and Chemistry, Manufacturing and Controls Reviewers. Please note that these comments are preliminary and reflect our review at this time. Additional comments will be provided as the reviews are finalized. These comments refer to the draft labeling identified as "31July03version," included in the "Proposed Labeling" section of the July 31, 2003 submission.

1. The sentences that previously read [redacted] have been changed to read "Improvement of lung function was maintained over 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance." [Lines 154-156]. The phrase [redacted] is somewhat ambiguous and might be taken to mean that the effect was established beyond 24 hours. Therefore the word ' [redacted] should be changed to "for."

2. Delete lines 172-177. Replace them with the following sentence: [redacted]

3. The following statements should be added to the CLINICAL PHARMACOLOGY section of the package insert: "In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline corrected QT interval of 30-60msec was higher in the tiotropium group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs. 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs. 1 (1%) patient] corrections of QT for heart rate."

4. In the CLINICAL PHARMACOLOGY, Mechanism of Action section: the word [redacted] (line48) has no particular meaning when used to qualify "antimuscarinic." Delete the word " [redacted]

5. In the CLINICAL PHARMACOLOGY, Mechanism of Action section: The following two sentences should be deleted: ' [redacted]

6. In the CLINICAL PHARMACOLOGY, Pharmacokinetics section: the first sentence [redacted] (Line 60) is not relevant to this section, and should be deleted. This same information is included in the DESCRIPTION section.

7. Replace lines 88-95 with the following text: "*In vitro* experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose

6. In the CLINICAL PHARMACOLOGY, Pharmacokinetics section: the first sentence (, (Line 60) is not relevant to this section, and should be deleted. This same information is included in the DESCRIPTION section.

7. Replace lines 88-95 with the following text: "*In vitro* experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving about 25% for metabolism) is metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4."

8. In the CLINICAL TRIALS section, line 146, delete the phrase "

9. In the CLINICAL TRIALS section, the population of patients studied should be more specifically defined. Add the following sentences at the end of the first paragraph (line 143): '

10. In the CLINICAL TRIALS section, the dosing schedule should be more explicit. In line 145, following the phrase "once-daily" add "in the morning".

11. The statement in the PRECAUTIONS section that ' Line 215) should be modified to read "Inhalation medications, including Spiriva, may cause paradoxical bronchospasm." This statement should be moved to the WARNINGS section of the label.

12. Add a statement in the PRECAUTIONS section of the label to

13. In the Drug Interactions section, the phrases "commonly used in COPD," and " are redundant. The second occurrence (line 243) should be deleted.

14. Add the following new paragraph in the Adverse Reactions section, following line 353: "In the one-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. (See **PRECAUTIONS, Geriatric Use)**

15. Modify the Adverse Event table to provide the incidences of specific adverse events in terms of the numbers of patients, in addition to the percentages.

(74% of an intravenous dose is excreted unchanged in the urine, leaving about 25% for metabolism) is metabolized by cytochrome P450 dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver microsomes showed that tiotropium in supra-therapeutic concentrations does not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4."

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12. Add a statement in the PRECAUTIONS section of the label to

13. In the Drug Interactions section, the phrases "commonly used in COPD," and " are redundant. The second occurrence (line 243) should be deleted.

14. Add the following new paragraph in the Adverse Reactions section, following line 353: "In the one-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age. (See **PRECAUTIONS, Geriatric Use)**

15. Modify the Adverse Event table to provide the incidences of specific adverse events in terms of the numbers of patients, in addition to the percentages.

16. The OVERDOSAGE section should include reference to a foreign post-marketing report of a case of overdose. This case was referenced in three separate submissions to the Agency (letters dated July 8, 2003, July 22, 2003, and September 29, 2003).

This was a female patient of unknown age from Australia, who was prescribed Spiriva for the treatment of COPD. She inhaled 30 capsules over a 2.5 day period and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, Spiriva was discontinued, and the constipation was treated with an enema. Further follow-up was not provided.

17. In the Dosage and Administration insert the following sentence after the sentence ending "...renally-impaired patients." (Line 384): "However, Spiriva use should be monitored closely in patients with moderate to severe renal impairment."

18. You have provided clarification that the trademark "Spiriva®" does not include the device. Therefore the name of the drug product should include the name of the device. Modify all labels and labeling to change the drug product name to the following name: "Spiriva® Handihaler® (tiotropium bromide inhalation powder)." This comment also pertains to the labels on the device. (Refer to your response to our comment 27 in your amendment dated December 16, 2003).

19. New suggested Pharmacology/Toxicology Labeling:

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 overestimated due to difficulties in measuring lung 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.

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 an inhalation dose of 0.009 mg/kg/day (approximately 4 times 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 overestimated due to difficulties in measuring lung doses in animal inhalation studies.

Pregnancy
Pregnancy Category C

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the 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's sexual maturation were observed at inhalation tiotropium doses of ≥ 0.078 mg/kg (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 0.4 mg/kg/day (approximately 360 times the RHDD on a mg/m^2 basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDD on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring lung doses in animal inhalation studies.

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

OVERDOSAGE

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats and 0.6 mg/kg in dogs. These doses correspond to 7,300, 120,000 and 850 times the recommended human daily dose on a mg/m^2 basis, respectively. These dose multiples may be overestimated due to difficulties in measuring in animal inhalation studies.

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/s/

Anthony Zeccola
12/23/03 02:55:20 PM
CSO

Memorandum of Teleconference

Date: 4/1/03

Application: N21-395 Spiriva (tiotropium bromide) Inhalation Powder

FDA Participants

Badrul Chowdhury, M.D., Ph.D., Division Director
Luqi Pei, Ph.D., Pharmacologist/Toxicologist
Guirag Poochikian, Ph.D., CMC Team Leader
Brian Rogers, Ph.D., Chemist
Eugene Sullivan, M.D., Clinical Team Leader
Joseph Sun, Ph.D., Pharmacology/Toxicology Supervisor
Anthony Zeccola, Regulatory Management Officer

Boehringer Ingelheim Participant
Neil Johnson (Toxicology)
Erhard Berkel (R & D coordination)
Stefan Heinrichs (Project Management)
Peter Fernandes (Regulatory)

Background: This teleconference was held in response to Boehringer Ingleheim's (BI) March 14, 2003, meeting request to discuss pending Pharmacology/Toxicology issues. The issues discussed included the calculation of dose ratios of tiotropium between animals and humans and degradation products in the drug substance and drug product.

Discussion:

1. Animal to Human Dose Ratios

   BI and the Division agreed to calculate the ratios between animals and humans using the following parameters: the delivered (or achieved) dose in the inhalation toxicity studies in animals and 18 mcg tiotropium/actuation in humans (i.e., 13.32 mcg/m^2). The delivered dose in animals will be based on the same form (e.g., free base or bromide salt) as what is present in the clinical formulations. The label will include a statement indicating that this exposure of tiotropium in animals is likely overestimated. BI will incorporate these changes in the draft label that will be included in the complete response to the December 20, 2002, Approvable letter.

2.a. Degradation Products [redacted]

   BI commits to the level of [redacted] in the drug substance to not-more-than [redacted] and the level of [redacted] in the drug product to not-more-than 1.0%. BI stated that these levels were within ICH limits. Dr. Rogers indicated that the actual

acceptance criteria will be based on the review of stability data and manufacturing capabilities.

2.b. Degradation Products [redacted]

BI accepted the Division's decision to consider the [redacted] compounds as degradants [redacted]

BI clarified that difference between [redacted] These [redacted] codes referred the same chemica[redacted]

A 13-week inhalation toxicity study of the degradants in rats was discusses. BI stated that it had initiated and completed a 13-week toxicology study of these degradants. The result will be available for submission shortly. Dr. Pei inquired whether this was a comprehensive toxicology study. Previous submissions indicated that only the respiratory tract would be examined microscopically. BI confirmed that this was a comprehensive study that a complete histology of all major organs of all animals was examined.

Regarding the timing of the submission of the study report, the Division informed BI that the Division had no preference as to whether the report is submitted to the IND or the NDA. Submission to the IND, will not guarantee a review prior to receipt of the complete response.

Submission of this study report post-approval, as proposed in earlier correspondence, is not acceptable.

BI has not set a specification for [redacted] yet, but it will be [redacted]

Additional Discussion Items

- Mr. Fernandes indicated that BI has submitted a [redacted] protocol for Division to comment, this protocol should arrive shortly.

- Mr. Fernandes indicated that the Safety update to be included with the complete response will have a data cut-off date of December 13, 2002. An additional safety update will be submitted during the review cycle. Dr. Sullivan said that the cut-off date of 12/13/02 might be acceptable, depending on the timing of the submission. He also reminded BI that the safety updates should include post-marketing data from countries where the drug is currently approved.

- Mr. Fernandes indicated that BI intends to submit the promotional materials for Spiriva during the review cycle, at around the same time that they submit the [redacted] stability data. The Division agreed that this is acceptable.

Post telephone conference action

After the teleconference, the pharmacology and toxicology review team discussed the necessity of establishing NOAELs for the degradants in the 13-week studies in rats. It was decided that this would be a review issue when the study is submitted.

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/s/

Anthony Zeccola
4/7/03 02:44:33 PM
CSO

Memorandum of Teleconference

Date: 3/24/03

Application: N21-395 Spiriva (tiotropium bromide) Inhalation Powder

FDA Participants
Guirag Poochikian, Ph.D., CMC Team Leader
Brian Rogers, Ph.D., Chemist
Anthony Zeccola, Regulatory Management Officer

Boehringer Ingelheim Participant
Dr. Stefan Heinrichs, International Project Leader, Spiriva
Dr. Burkhard Blank, Senior Vice President, Medical and Drug Regulatory Affairs
Dr. Marty Kaplan, Vice President, Drug Regulatory Affairs
Dr. Steve Horhota, Highly Distinguished Fellow, Pharmaceutics R&D
Mr. Peter Fernandes, Director, Drug Regulatory Affairs
Ms. Eileen Wyka, Director, Technical Drug Regulatory Affairs

Background: This teleconference was scheduled as a continuation of the teleconference between representatives of Boehringer's Ingelheim's (BI) and the Division of Pulmonary and Allergy Drug Products, which took place on March 20, 2003. The purpose of this teleconference was to discuss the details regarding th[redacted]capsule per blister card configuration and the stability data to support this packaging that would be including in the complete response (CR) to the December 20, 2002 Approvable letter.

Discussion: Dr. Rogers opened the discussion by summarizing the type of in-use data that would be required to support submission of the [redacted]

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/s/

Anthony Zeccola
4/7/03 02:11:03 PM
CSO

Memorandum of Teleconference

Date: 3/20/03

Application: N21-395 Spiriva (tiotropium bromide) Inhalation Powder

FDA Participants
Guirag Poochikian, Ph.D., CMC Team Leader
Brian Rogers, Ph.D., Chemist
Eugene Sullivan, M.D., Acting Clinical Team Leader
Anthony Zeccola, Regulatory Management Officer

Boehringer Ingelheim Participant
Burkhard Blank, M.D., Senior Vice President, Medical and Drug Regulatory Affairs
Martin Kaplan, M.D., J.D., Vice President, Drug Regulatory Affairs

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Background: This teleconference was in response to Boehringer's Ingelheim's (BI) February 25, 2003 submission. The focus of this teleconference was discussion of the configuration of the — packaging of the tiotropium capsules. BI has proposed a configuration of —capsules per blister, rather than the —capsules per blister as submitted in the original NDA and has requested comment on this proposal.

Discussion: Dr. Poochikian opened the discussion by stating that the —capsule per blister card is not optimal. The Division would prefer a configuration that would be —, but an interim solution that would permit approval of this configuration might be possible.

Dr. Kaplan acknowledged that BI is aware of the Agency's position on the various proposed configurations and stated that BI is actively pursuing alternative packaging configurations. BI has not yet arrived at the optimal solution, so they are unable to provide a projected implementation date at this time, but they would be willing to provide such a timeline commitment during the next several months.

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/s/

Anthony Zeccola
3/25/03 11:10:42 AM

Memorandum of Teleconference

Date: 10/21/02

Location: Zeccola's Office

FDA Participants
Luqi Pei, Ph.D., Pharmacology/Toxicology Reviewer
Anthony Zeccola, Regulatory Management Officer

Boehringer Ingelheim Participant
Peter Fernandes, M. Pharm, Directory, Drug Regulatory Affairs

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Background:

The following questions was posed by Mr. Fernandes via email:

1. The safety factor used in our labeling were based on the "achieved dose" in the animal studies compared to the human dose (0.45 mcg/kg based on a 22.5 mcg dose for a 50 kg individual). This calculation we understand has been used for other labeling e.g., Salmeterol.

2. Based on our rough calculations, it appears that FDA may have used the "theoretical animal lung dose" for the animals and the "total human dose" (not the corresponding theoretical human lung dose which is about 3.65 mcg). This may be one reason why the revised correlation to the human dose is low.

Discussion:

Dr. Pei indicated that BI was correct in understanding our approach in calculating the dose ratios between animals and humans. The Division used the theoretical pulmonary deposits as an estimate of animal exposure and assumed 100% of the clinical dose as human exposure. The Division used the same factors that BI had used to derive the estimated pulmonary deposits in animals. Dr. Pei also pointed out that BI had applied the deposition factor for all inhalation toxicity studies except for the carcinogenicity studies.

Mr. Fernades indicated that they would like to use delivered dose (from the mouth piece) in the calculation of exposure. Dr. Pei indicated that in order to do this, they would need to submit their rationale along with supporting data.

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/s/

Anthony Zeccola
10/22/02 08:52:05 AM
CSO

Luqi Pei
10/23/02 10:25:09 AM
PHARMACOLOGIST

Memorandum of Telephone Facsimile Correspondence

Date: November 30, 2003

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Eugene Sullivan, M.D.

Through: Anthony M. Zeccola

Subject: Medical Officer Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

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Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

The Summary of Safety describes analyses of centralized readings of ECGs performed in Study 205.131. These analyses reveal that the number of subjects with changes from baseline QTcB and QTcF of 30-60msec was notably higher in the tiotropium group, as compared to placebo (Summary of Safety, page 50). For instance, 16 (16.3%) patients treated with tiotropium and 1 (1%) patient treated with placebo had changes of this magnitude in QTcF. Comment on the potential clinical significance of this observation and provide a proposal to further investigate possible QTc effects of tiotropium.

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/s/

Anthony Zeccola
11/30/03 12:51:00 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: November 30, 2003

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Alan Schroeder, Ph.D.

Through: Anthony M. Zeccola

Subject: CMC Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

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Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

Provide representative certificates of analysis for the aluminum foil used by your supplier to make the lidding foil and [redacted] identified as " [redacted] ' and

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/s/

Anthony Zeccola
11/30/03 12:46:04 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: November 18, 2003

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Alan Schroeder, Ph.D.

Through: Anthony M. Zeccola

Subject: CMC Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

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Thank you.

{See appended electronic signature page}

Anthony M. Zeccola, M.A.
Senior Regulatory Management Officer
Division of Pulmonary Drug Products

This comment pertains to the degradant [redacted] which you have indicated to be [redacted] Please indicate the source of the [redacted] in the drug product.

Provide any data that you have for the *individual* degradant levels for [redacted] in the drug product after [redacted] of stability storage.

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/s/

Anthony Zeccola
11/18/03 12:38:23 PM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: October 25, 2002

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Luqi Pei, Ph.D.

Through: Anthony M. Zeccola

Subject: Pharmacology/Toxicology Comments – NDA 21-395

Total Pages: 3 including this page and electronic signature page

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Luqi Pei., Ph.D.
Pharmacology/Toxicology Reviewer
Division of Pulmonary Drug Products

The following comment is pertinent to the 18mcg drug product:

Lower the levels of [redacted] (each) in the drug product to not-more-than 1.0%, or conduct a comprehensive 13-week inhalation toxicity study of these degradants in an animal species. The testing material of the study may be either a mixture of the degradants only or tiotropium spiked with the degradants. The level of exposure for each degradant in animals must be high enough to provide a sufficient safety margin over the expected human exposure. The study should establish a NOAEL for these compounds.

The following comment is pertinent to tiotropium bromide drug substance:

Lower the level of [redacted] in the drug substance to not-more-than 0.1%, or establish a 13-week inhalation NOAEL for [redacted] The establishment of a 13-week NOAEL may be accomplished by completing histological evaluation of the low- and mid-dose groups of Study U97-2187. Another 13-week inhalation study of [redacted] is needed, should the reanalysis of Study U97-2187 fail to identify the NOAEL for the compound.

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/s/

Anthony Zeccola
10/25/02 12:04:59 PM
CSO

Luqi Pei
10/25/02 12:07:47 PM
PHARMACOLOGIST

Memorandum of Telephone Facsimile Correspondence

Date: July 26, 2002

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Badrul Chowdhury, M.D., Ph.D.

Through: Anthony M. Zeccola

Subject: Request for Information – NDA 21-395

Total Pages: 3 including this page and electronic signature page

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Badrul Chowdury, M.D., Ph.D.
Acting Director
Division of Pulmonary Drug Products

For the combined data from the two one-year, placebo-controlled studies provide shift tables indicating the number (and percent) of patients exhibiting a specific increase in heart rate at each test day. Provide such tables for increases of 5, 10, 15, and 20 beats per minute.

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/s/

Anthony Zeccola
7/26/02 02:03:55 PM
CSO

Badrul Chowdhury
7/26/02 02:25:40 PM
MEDICAL OFFICER

Memorandum of Telephone Facsimile Correspondence

Date: July 22, 2002

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Badrul Chowdhury, M.D., Ph.D.

Through: Anthony M. Zeccola

Subject: Request for Information – NDA 21-395

Total Pages: 1 (2 including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Badrul Chowdury, M.D., Ph.D.
Acting Director
Division of Pulmonary Drug Products

Please a provide a discussion of the number of pregnancies that occurred during the clinical studies of tiotropium bromide, and the outcome of the pregnancies, if any.

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/s/

Anthony Zeccola
7/19/02 02:32:08 PM
CSO

Eugene Sullivan
7/19/02 02:35:43 PM
MEDICAL OFFICER

Badrul Chowdhury
7/19/02 05:05:14 PM
MEDICAL OFFICER

Memorandum of Telephone Facsimile Correspondence

Date: July 19, 2002

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Badrul Chowdhury, M.D., Ph.D.

Through: Anthony M. Zeccola

Subject: Request for Information – NDA 21-395

Total Pages: 2

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

{See appended electronic signature page}

Badrul Chowdury, M.D., Ph.D.
Acting Director
Division of Pulmonary Drug Products

Please provide the following information to assist in our review of NDA 21-395:

In regard to Study 205.131:

1. The exercise parameters were similar between groups at Day –15 and Day –10. However, on Day –5, the endurance time was notably greater in the placebo group. Explain why this might have occurred. Do you believe that this was an aberrant, chance observation or does it represent a "failure of randomization" (i.e. an indication that there was a baseline difference between treatment groups that was present despite randomization)?

2. For the primary efficacy variable (endurance time at Day 42), provide a non-log transformed analysis of covariance using Day –10 as baseline instead of Day –5. Also provide non-log transformed and log-transformed analyses of covariance without including baseline as a covariate.

3. Provide the same data for the endurance time at Day 21.

4. Given the known pharmacodynamic properties of the drug, explain why the treatment effect, in regard to endurance time, would be so much greater on Day 42, as compared to Day 21.

5. Provide the IND submission dates for the original protocol and all protocol amendments.

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/s/

Anthony Zeccola
7/18/02 04:35:48 PM
CSO

Eugene Sullivan
7/19/02 07:29:24 AM
MEDICAL OFFICER

Badrul Chowdhury
7/19/02 08:43:02 AM
MEDICAL OFFICER

Memorandum of Telephone Facsimile Correspondence

Date: 06/19/02

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Anthony Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products
FDA

Subject: Request for Information – NDA 21-395

Total Pages: 3 (Including this page and electronic signature page)

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products

Please provide the following information to assist in our review of NDA 21-395:

1. For Studies 205.114/205.117 and 205.115/205.128: The original protocol indicates that "peak flow *and* FEV_1 measurements will be recorded *three times daily* by the patient throughout the 54-week evaluation period including the two-week baseline period and one-year treatment period." [file: U99-3169.pdf, page 306]. This was subsequently changed in Amendment 1 to two times daily. However, the reference to FEV_1 was not removed [file: U99-3169.pdf, page 353]. Did the patients measure and record FEV_1 values at home? If so, has that data been analyzed?

2. In Studies 205.114/205.117 and 205.115/205.128 a number of ECGs were performed during the treatment period. When were the ECGs obtained, in relation to dosing of study medication (i.e. pre-dose, or at a specified interval following dosing)?

3. In Studies 205.114/205.117 and 205.115/205.128, serial spirometry was performed at 30, 60, 120, and 180 minutes post-dosing at several study visits. For each study, provide the following information for each visit at which serial spirometry was performed: The number of patients who reached their peak FEV1 at each post-dosing time point.

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/s/

Anthony Zeccola
6/19/02 11:34:59 AM
CSO

Memorandum of Telephone Facsimile Correspondence

Date: 03/07/02

To: Peter Fernandes
Director, Drug Regulatory Affairs

From: Anthony Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products
FDA

Subject: Request for Information – NDA 21-395

Total Pages: 3

We are providing the attached information via telephone facsimile for your convenience, to expedite the progress of your drug development program. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

Thank you.

Anthony M. Zeccola
Regulatory Management Officer
Division of Pulmonary Drug Products

Please provide the following information to assist in our review of NDA 21-395:

1. In Studies 205.130 and 205.137 you used a salmeterol MDI and salmeterol placebo MDI. Please provide us with the source of these products, their compositions, and physical properties (plume geometry, particle size, etc.) if known.

2. Provide the rules used for the calculation of intent-to-treat values for the primary efficacy analysis of TDI?

3. In the dataset for Study 205.137, there is an investigator — who is not listed among your table of investigators in volume 124 pages 31-34 (bottom page numbers). Explain.

4. Provide derived data sets for Studies 205.130, 205.137, 205.117 and 205.128 from which the primary and important secondary efficacy analyses (trough FEV_1, TDI, and COPD symptoms) can be easily performed. The following provides a suggestion of what these data sets might look like. The datasets should contain regular visit values and carry forward values, Visit ID, centers (using center numbers), centers after pooling, baseline values, treatment code, indicator variable whether value was a carry forward value, another indicator variable giving type of carry forward value (i.e. last visit, worst value, etc.). The last two could possibly be combined. Also include indicator random variables that tell whether the patient was included in the respective ITT analyses. For the dataset containing TDI there should be an indicator variable whether patient was a responder or not. Provide similar datasets for Studies 205.126A and 205.125B (the two Atrovent controlled studies) for trough FEV_1 and TDI.

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/s/

Anthony Zeccola
3/7/02 02:55:30 PM
CSO

Anthony Zeccola
3/7/02 02:56:24 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II

FACSIMILE TRANSMITTAL SHEET

DATE: December 19, 2003

To: Ms. Eileen Wyka, Director, Technical Drug Reg. Affairs	**From:** Anthony M. Zeccola, Senior Reg. Management Officer
Company: Boehringer Ingelheim Pharmaceuticals, Inc.	Division of Pulmonary and Allergy Drug Products
Fax number: 203-791-6262	**Fax number:** 301-827-1271
Phone number: 203-778-7714	**Phone number:** 301-827-1058

Subject: CMC Request for Information – NDA 21-395

Total no. of pages including cover: 4

Comments:

Document to be mailed: YES xNO

Your NDA 21-395 is currently under review and we have the following request(s):

The following comments pertain to our letter dated November 7, 2003 and your response dated December 4, 2003. These comments are cross-referenced in parentheses, to the comments in our November 7, 2003, letter.

1. In view of the lack of drug product stability data for significantly different particle size distributions (PSDs) of the [redacted] drug substance, modify your acceptance criteria for [redacted] drug substance PSD to agree with that requested by the Agency in our December 20, 2002 letter, as you have proposed. (Comment 2)

2. Provide an agreement to continue to monitor the PSD of the [redacted] drug substance after [redacted] and to investigate and rectify any unusual variability, and discuss it with the Agency. (Comments 4 and 5)

3. Modify your acceptance criteria for delivered dose uniformity for the drug product as follows, based upon your data (Comment 11):

[redacted]

4. *Modify and resubmit the aerodynamic particle size distribution (APSD) mass* balance criteria and mass balance data to support your proposal for the drug product, taking into account the following points (Comment 13):

   a. Calculate mass balance based entirely on emitted dose from the mouthpiece, relative to the labeled claim quantity of emitted dose.

   b. Indicate the number and percentage of data points for mass balance in your original primary NDA stability data which are outside of — of label claim for the emitted dose, based upon the response to comment 4a, above.

   c. For failures of the proposed acceptance criteria for mass balance (i.e., *any* value outside of the range of the acceptance criteria), perform a thorough investigation of the analytical method and the performance of the cascade impactor (e.g., including number and dimensions of jet holes for each stage). If the investigation indicates that there was an analytical failure, rectify it and retest *once* with a larger number of samples.

   d. If there is any suggestion that the mass balance failure is due to the drug product, such potential failure should be assessed by further testing. If drug product failure is confirmed, these results should be discussed with the Agency.

5. Provide evidence to demonstrate that — lidding foil proposed in the original NDA provides equivalent seal seam strength to the current to-be-marketed lidding foil proposal — and that seal seam strength is equivalent for both the standard and dedicated packaging lines, or that the to-be-marketed foil seal is better. Use a single method to provide these data. (Comment 16c and e)

6. On your specification sheet for the HandiHaler, define the various defect classes listed under "acceptance criteria." (Comment 17c)

7. You are reminded that DMF — remains deficient. (Comment 19)

8. Placement of the labeling on the outer carton is not an option. An interim solution for devices already manufactured as of the date of our last letter, is that a sticker containing the appropriate labeling may be attached to the device. We recommend that the long term solution should involve printing the labeling onto the device. The proprietary name should be modified as follows: "Spiriva® HandiHaler® (tiotropium bromide inhalation powder)." (Comment 20)

9. Clarify why certain analytical procedures in the revised stability protocol do not have a method number but are listed as "TBD." Rectify this. (Comment 24a)

We have the following additional comments.

10. Provide the following modification to the acceptance criteria for lactose:

11. Clarify the testing that you perform for acceptance of drug product components, the testing which is routinely accepted on a certificate of analysis from the manufacturer, and the frequency of testing that you perform to periodically verify the results on the certificates of analysis.

12. Provide a comprehensive summary of all commitments/agreements that you have made for this NDA.

13. Submit updated specification sheets, SOPs, and other relevant manufacturing and control documents in accordance with the changes proposed in your amendment dated July 31, 2003 and subsequent amendments.

You are reminded of our comments in our second information request letter, dated December 10, 2003, and the comment faxed to you on November 30, 2003.

If there are any questions, please contact Anthony Zeccola, Project Manager, at 301-827-1058.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Anthony Zeccola
12/19/03 11:33:27 AM
CSO

4 Page(s) Withheld

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-395	Efficacy Supplement Type SE-	Supplement Number	
Drug: Spriva® (tiotropium bromide) Inhalation Powder		Applicant: Boehringer Ingleheim Pharmaceuticals, Inc.	
RPM: Zeccola		HFD-570	Phone # 827-1058
Application Type: 505(b)(1) (X) 505(b)(2) ( )		Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3
• Other (e.g., orphan, OTC)	N
❖ User Fee Goal Dates	13-Oct-2002
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	( ) Verified

Exclusivity (approvals only)	
• Exclusivity summary	
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	
General Information	
❖ Actions	
• Proposed action	( ) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DMRTS Review 2/22/02
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	
• Reviews	
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	

Advisory Committee Meeting	
• Date of Meeting **9/6/02**	
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9/17/02
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	10/rt
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Statistical review(s) *(indicate date for each review)*	
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9/18/02
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9/18/02
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)* c/t consult 8/28	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	
• Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	9/20/02
❖ Nonclinical inspection review summary	NA
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	In 9/20/02 Rev
❖ CAC/ECAC report	7/8/02

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

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

2. TELEPHONE NUMBER *(Include Area Code)*

(203) 798-5337

3. PRODUCT NAME

SPIRIVA® (tiotropium bromide) Inhalation Powder

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021395

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4162

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY
(Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Peter Fernandes	Director, Drug Regulatory Affairs	November 14, 2001

FORM FDA 3397 (4/01)

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14 Draft Labeling Page(s) Withheld