CENTER FOR DRUG EVALUATION AND *RESEARCH*

APPLICATION NUMBER:

21-395

ADMINISTRATIVE DOCUMENTS

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

DA/BLA # : 21-395 Supplement Type (e.g. SE5): _____ Supplement Number:

Stamp Date: August 1, 2003 Action Date:

HFD 570 Trade and generic names/dosage form: Spiriva HandiHaler (tiotropium bromide inhalation powder

Applicant: Boehringer Ingleheim Therapeutic Class:

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

ection A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- X Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed

☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____ kg____ mo.____ yr.____ Tanner Stage____
Max____ kg____ mo.____ yr.____ Tanner Stage____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 21-395
HFD-960/ Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

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/s/

Anthony Zeccola
1/16/04 05:10:03 PM

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/BLA # 21-395 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-570 Trade and generic names/dosage form: Spiriva (tiotropium bromide) Action: AE AE NA

Applicant Boehringer Ingleheim Pharmaceuticals, Inc. Therapeutic Class _____

Indication(s) previously approved _____

Pediatric information in labeling of approved indication(s) is adequate X inadequate _____

Proposed indication in this application Chronic Obstructive Pulmonary Disease

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ___No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) ____Infants (6 month-2yrs) _____Children (2-12yrs) ____Adolecents(12-16yrs)

___ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

____3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing,

___ (2) Protocols were submitted and approved.

___ (3) Protocols were submitted and are under review.

___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

X 4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

Note: Please Refer to the Medical Officer Review, Page 79 .

5. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? __ Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer's Review (e.g., medical review, medical officer, team leader)

LSK

Signature of Preparer and Title

23-Sept-02

Date

cc: Orig NDA #21-395
HFD-570/Div File
NDA/BLA Action Package
HFD-960/ Peds Team
(revised 1-14-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960, 4-7337

ITEM 14 Patent Certification

Original Declaration with respect to a formulation, composition or method of use patent

The undersigned declares that Patent No. 5,610,163 covers the formulation, composition, and/or method of use of SPIRIVA® (tiotropium bromide) Inhalation Powder. This product is the subject of this application for which approval is being sought.

By: _____
Mary Ellen Devlin

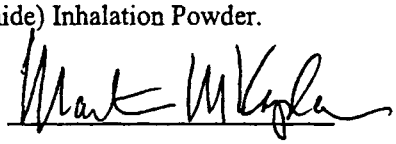
Capacity: ☐ Applicant's Agent (Representative)
☒ Applicant's Attorney

Date: November 19 2001

Item 16 Debarment Certification

Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)(1)

The undersigned certifies that Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and Cosmetic Act in connection with SPIRIVA® (tiotropium bromide) Inhalation Powder.

Signature: 

Name of the Applicant: Martin M. Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 25 Sept 2002

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

Item 16 Debarment Certification

Certification Requirement Section 306(k)(1) of the Act 21 U.S.C. 355a(k)(1)

The undersigned certifies that, to the best knowledge and belief of the undersigned, Boehringer Ingelheim Pharmaceuticals, Inc. did not and will not use in any capacity the services of any person debarred under subsection (a) or (b) [Section 306(a) or (b)] of the Federal Food, Drug and Cosmetic Act in connection with SPIRIVA® (tiotropium bromide) Inhalation Powder.

Signature: Mart M Kaplan

Name of the Applicant: Martin M. Kaplan, M.D., J.D.
Vice President, Drug Regulatory Affairs
Boehringer Ingelheim Pharmaceuticals, Inc.

Date: 2 November, 2001

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

Need
New
Debarment

Office Director's Sign-Off Memorandum

Date:	Friday, January 30, 2004
NDA:	21-395
Sponsor:	Boehringer-Ingleheim
Proprietary Name:	Spiriva (tiotropium bromide Inhalation Powder) HandiHaler

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Introduction: This is the second cycle for this application, a new molecular entity being developed as a bronchodilator for the treatment of COPD. Please see my prior memo of December 20, 2002, and other reviews for details.

The application was not approved in the first cycle largely due to issues related to CMC.

CMC: The numerous issues previously addressed in our action letter of 2002 have all been satisfactorily addressed now. There are some post-marketing agreements that will further hone the CMC aspects of this product, but none of these preclude marketing at this time.

Final recommendations from Compliance on the EERs is that the various sites involved in the production and testing of this product are acceptable as of this time.

Pharm/Tox: The sponsor attempted to qualify some impurities with an inhalation toxicology study of these impurities. However, due to issues of particle sizing, the exposure in the animals was not sufficient to achieve the desired 10-fold exposure ratio to humans, though no toxicity was seen. Given no toxicity was seen and given the conservative exposure ratio we normally expect, I believe the product can be approved with the proposed limits on these impurities, but the sponsor will need to and has agreed to conduct a satisfactory qualification study post-approval.

Biopharmaceutics: No new issues.

Clinical / Stastical: Except for labeling, no new issues were raised by the resubmission. It is notable that late in the review cycle, we received a call from BI about a rise in the number of post-marketing deaths being reported. The total number of deaths that BI has seen for tiotropium in the last 12 months was 282. This contrasts with approximately 40 deaths that were reported in the previous 12 month time period. It is notable that within and prior to the most recent time period, the drug was launched in many countries and some trials are also ongoing.

The breakdown of the 282 deaths are as follows:

1. Spontaneous reports: 83
2. Reports by health agencies: 10
3. Observations studies: 122
4. Controlled studies: 67

Of the deaths that would be most informative, the controlled study deaths do not show an excess of deaths with Spiriva compared with active and placebo controls. As the COPD

population has a fairly high mortality rate, it would not be unexpected to have associated deaths, even if not causally linked and reporting tends to be higher immediately post-approval. This will bear watching post-approval in the US, but does not appear to be a significant concern.

A second issue, new this cycle, was the results of a good QT study done in the exercise setting. Tiotropium would not be predicted pharmacologically to have any effect nor was one seen in routine ECG monitoring (albeit these were not definitive studies for determining ECG intervals). The exercise study did not show a remarkable mean effect of tiotropium on QTc compared to placbo. However, there were more outliers with tiotropium (16 – 20% depending on correction method) than control (1-12%). Though potentially anomalous, this will be mentioned in labeling along with the other available data and a further study will be conducted post-approval to either better delineate any such [redacted] to refute the concern (and hence remove these observations from the labeling).

Labeling and nomenclature: Satisfactory labeling was negotiated with the sponsor prior to action, though some package labeling will be revised post-approval to implement a portion of DMETS's recommendations. DDMAC, [redacted]

Regulatory Conclusions: This product will be approved with post-marketing commitments for a further toxicology study of degradants/impurities and a clinical study of QT effects. There are also some post-marketing agreements for CMC and some post-approval changes in the package labeling.

Robert J. Meyer, MD
Director,
Office of Drug Evaluation II

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/s/

Robert Meyer
1/30/04 04:27:34 PM
MEDICAL OFFICER

Office Director's Sign-Off Memorandum

Date:	Friday, December 20, 2002
NDA:	21-395
Sponsor:	Boehringer-Ingleheim
Proprietary Name:	Spiriva (tiotropium bromide) Inhalation Powder

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Introduction: This is a first-cycle application for this drug product, a new molecular entity being developed as a bronchodilator for the treatment of COPD. It is an inhalation powder packaged in individual gelatin capsules that are loaded one at a time in an inhaler device specifically designed for this drug – the HandiHaler. The dose proposed is 18 mcg inhaled once daily. Tiotropium is an anticholinergic, muscarinic agent related to ipratropium, but with a substantially longer bronchodilatory action. Additionally, the sponsor wished to claim an effect of the drug on dyspnea (see below), which would be a unique claim for such an agent in COPD.

I refer the reader to the summary memorandum of Dr. Chowdhury for detailed discussions. However, this memorandum will serve to highlight a few salient and or additional points stemming from the Office Director's review.

CMC: At the time of the review of the package, the CMC review is still being tertiary reviewed by Dr. Eric Duffy. However, there are many issues relating to the drug substance, product and packaging that need resolution prior to this drug receiving approval for marketing. None of these issues appear to be of such severity that they could not be adequately addressed by the sponsor in the next cycle.

Final recommendations from Compliance on the EERs is that the various sites involved in the production and testing of this product are acceptable as of this time.

Pharm/Tox: This drug has been adequately tested in acute, subchronic and chronic studies, including inhalation toxicology since most of the exposure to animals was inhalational. The sponsor has also provided reproductive toxicology and carcinogenicity studies. The drug is relatively non-toxic and the animal data to not suggest any undue signals of toxicity that need special attention in the human trials/marketing. The drug is not mutagenic or clastogenic and was negative in carcinogenicity studies. However, it will be labeled as pregnancy category 'C' due effects on fertility and fetal viability and growth..

Biopharmaceutics: The absolute bioavailability of tiotropium was about 20% inhaled, with only 2 – 3 % oral bioavailability, suggesting that most of the tiotropium that enters the blood does so from the lungs and since inhalation dosage forms (like DPIs) generally only have about a 25% efficiency, this implies that most of the tiotropium delivered to the lungs is eventually absorbed. The drug is renally-cleared by and does not appear to be metabolized by the P450 system to any relevant degree. As might be expected from this, clearance of the drug decreases with age and in renal impaired patients, there will be need for caution due to increased exposures at clinical doses. See Dr. Kim's review for details.

Clinical / Stastical: Dr. Sullivan and Dr. Kammerman did excellent reviews of the clinical trials data, and I refer the reader to those reviews. However, the sponsor provided data from six pivotal phase 3 trials, after choosing a dose based on earlier dose-ranging trials. The Division agreed with the proposed phase 3 dose at an end-of-phase 2 meeting in 1996. These six trials included patients with reasonable clinical definitions of COPD, who were treated either for one year or six-months, depending on the trials. Also, positive controls of either ipratropium or salmeterol were variably used in these trials. The results of these trials clearly show a substantial, durable bronchodilation with tiotropium given once daily. The drug appears clearly superior to ipratropium dosed four times a day and similar if not somewhat superior in some aspects to salmeterol given twice daily. However, for reasons of trial design and results, the sponsor did not substantiate their claim of a clinically important effect on dyspnea.

For safety, over 1100 patients were enrolled in the phase 3 trials, giving a large, controlled database with exposures of 6 to 12 months. Overall, the drug appears acceptably safe for the use proposed, given its effects. Although there is a very weak signal of more cardiac mortality in patients on tiotropium compared to control, these was no overall excess mortality in the tiotropium arms. Otherwise, the most notable events were predictable – anticholinergic events such as urinary retention, dry mouth, ... These events were not at high rates, however. There were also fairly common complaints of GI interolerance (upwards of 5% of patients for events like dyspepsia or abdominal pain). In holter monitor testing, there was no evidence of untoward effects of tiotropium compared to placebo, though one set of 1-year studies showed a slight imbalance in the reporting of heart rate/arrhythmias than placebo (4.2% vs. 2.2%). This was not seen in the other sets of studies, however.

It is notable that the population study was restricted as to active cardiac disease, as well as excluding diseases that might be exacerbated by an anticholinergic, like benign prostatic hypertrophy and narrow angle glaucoma.

An advisory committee meeting was held on this product, and the committee recommended approval for this drug without the dyspnea claim. They suggested the need for further data phase 4 in more generalized populations, particularly focusing on the cardiac and urinary issues.

Labeling and nomenclature: Most labeling was satisfactorily negotiated with the sponsor prior to action. Some issues (such as representing the comparators in the Clinical Trials subsection) will need to be further discussed with the sponsor prior to approval..

Regulatory Conclusions: This product will be given an 'Approvable' action at this point, due to CMC considerations.

Robert J. Meyer, MD
Director,

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/s/

Robert Meyer
12/20/02 03:30:52 PM
MEDICAL OFFICER

DIVISION DIRECTOR'S MEMORANDUM

Date: December 17, 2002

To: NDA 21-395

From: Badrul A. Chowdhury, MD, PhD
Acting Director, Division of Pulmonary and Allergy Drug Products

Product: Spiriva (tiotropium bromide) Inhalation Powder

Applicant: Boehringer Ingleheim Pharmaceuticals, Inc.,

Introduction

Boehringer Ingleheim Pharmaceuticals, Inc., (BIPI) submitted NDA 21-395 for Spiriva (tiotropium bromide) Inhalation Powder on December 12, 2001, for the treatment of chronic obstructive pulmonary disease (COPD). The regulatory pathway for this application is 505(b)(1). Pfizer will be a co marketer of this drug with BIPI when approved. The user fee goal date for an action on this application was October 13, 2002. The action on this application is taken past the due date because the chemistry review and the evaluation of manufacturing establishments were not completed by the due date. As of the date of this application no formulation of tiotropium was approved for any indication in the United States or elsewhere in the world.

The Division of Pulmonary and Allergy Drug Products met with BIPI at various stages of the development program of tiotropium bromide. Some significant meetings were an end-of-phase 2 meeting held on December 3, 1996, a pre-NDA meeting held on May 10, 1999, to discuss the chemistry portion of the NDA, and another pre-NDA meeting held on May 12, 1999, to discuss the pre-clinical and clinical portions of the NDA. The Division also met with BIPI on July 24, 2000, to discuss BIPI's proposal to change dyspnea endpoint in two completed studies from secondary endpoint to co-primary endpoint to support an indication of dyspnea for Spiriva Inhalation Powder. Minutes of these meetings are in the Division file.

Tiotropium inhalation powder is an anticholinergic bronchodilator intended for oral inhalation. All drugs currently approved in the Unites States for COPD are bronchodilators. These include short acting beta2-adrenerig agonists albuterol, bitolterol, metaproternol, pirbuterol, and terbutaline; long acting beta2-adrenergic agonists salmeterol and formoterol; short acting anticholinergic agent ipratropium; and theophylline. Theophylline is an exception to the list above. Theophylline mentions "symptoms and reversible airflow obstruction" in the "indications and usage" section of the label. Theophylline is a relatively older drug and did not undergo rigorous pre-approval clinical testing as would be required to satisfy the current standards. The drugs currently approved for COPD are available primarily as metered dose inhalers and solutions for oral inhalation. The approval of Spiriva would provide the physicians and

patients another choice for the treatment of COPD, and would represent first once-daily oral inhalation drug for the treatment of COPD.

BIPI's proposed indication for Spiriva Inhalation Powder included dyspnea in addition to bronchospasm associated with COPD. The proposed indication of dyspnea is unique for a COPD drug. A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was conveyed on September 6, 2002, to discuss the proposed dyspnea indication, and to discuss the overall efficacy and safety data of Spiriva Inhalation Powder.

Chemistry, Manufacturing, and Controls (CMC)

Spiriva consists of a gelatin capsule containing a dry powder for use with the HaldiHaler inhalation device. Each capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate as the carrier.

The drug substance, tiotropium bromide, is a synthetic, non-chiral, quaternary ammonium compound. It is synthesize

The drug product is a hard gelatin capsule containing a mixture of the drug substance and the carrier lactose. The capsules are sealed in moisture-resistant aluminum foil blisters. The blister consists of three components, an aluminum based peelable lidding foil, a polyvinyl chloride forming film, and a aluminum based bottom foil material. One blister card contains capsules.

The HandiHaler is a reusable, hand-held, breath-actuated inhalation device designed to be used with the Spiriva capsule. To administer a dose, the patient opens the HadiHaler, places a capsule into the capsule chamber, closes the mouthpiece, pressed the button, and then inhales through the mouthpiece. Pressing the button causes two needles to pierce the capsule. Inhalation through the mouthpiece causes the pierced capsule to vibrate, aerosolizing the contents of the capsule. Although the capsule contains 18 mcg of drug substance, the HandiHaler delivers approximately 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 6.2 seconds.

The drug product has tiotropium impurities and degradants above the acceptable limits (ICH quantification thresholds). These are , each at up to , in drug product. To support the level of these impurities and degradants in the tiotropium product, BIPI has conduced at two genetic toxicology assays with each of these compounds. BIPI has also conducted a 13-week inhalation toxicity study with the drug substance impurity, and a 4-week inhalation toxicity study with the drug product degradants. Pharmacology-Toxicology reviewer Dr. Luqi Pei reviewed these pre-clinical studies and concluded the following: 1) All genotoxicity assays were negative. 2) The drug substance impurity mostly possessed a toxicologic profile of cholinergic agents. 3) The drug product impurities at the tested levels did not cause any additional damages that were attributed to the co-administered tiotropium. Dr. Pei also concluded that the 13-

week study failed to establish a No-Observed-Adverse-Effect Level (NOAEL) that was necessary for determining an acceptable limit for the drug substance impurity. The 4-week study was insufficient to support the levels of the drug impurities. Dr. Pei recommended that the applicant should lower the level of drug substance impurity to not more than 0.1% or establish a 13-week inhalation NOAEL for the drug substance impurity; and lower the level of drug product degradants to not more than 1% or conduct comprehensive 13-week inhalation toxicity study of these in an animal species. These comments were communicated to the applicant by facsimile on October 25, 2002.

The CMC reviewer has identified various deficiencies that need to be resolved before this application can be approved, and I concur with those. The deficiencies relate to drug substance and drug product manufacturing and specifications.

Establishment Evaluation

The primary site of drug substance manufacturing, packaging, release and stability testing is a Boehringer Ingelheim facility in Ingelheim, Germany. The drug substance will also be manufactured in a facility in [redacted]
The finished dosage manufacturer is a facility in [redacted]
dosage will be tested in facilities in [redacted] These facilities have been evaluated and have acceptable status.

Pharmacology and Toxicology

The preclinical evaluation of tiotropium included in vitro receptor binding studies, non-clinical pharmacology and pharmacokinetic studies, general toxicity studies, reproductive toxicity studies, genetic toxicity studies, and carcinogenicity studies. Dr. Luqi Pei has reviewed these studies in detail, and has recommended an approval action from a non-clinical perspective and I concur with that recommendation. The salient non-clinical findings are summarized in the following paragraphs.

The in vitro binding studies suggested preferential occupation of the muscarinic M3-receptor over the M1- and M2-receptors.

Single and multiple dose general toxicology studies were performed primarily in the rat and the dog. Inhalation, the intended clinical route of administration, was used in most animal toxicity studies. Inhaled drug was rapidly observed in both species. Some multiple dose studies were conducted for period of up to 12 months. General toxicity studies showed that the gastrointestinal tract and the secretory glands were the primary target organs of toxicity. Other organs involved were the eye, respiratory tract, heart, and the urinary bladder. Notable toxicological findings in the animal studies included anticholinergic effects such as increase in heart rate, decreased gastrointestinal motility, decreased production of tear and saliva, and mydriasis. An interesting species specific observation was the proteinaceous deposits in the urinary bladder in male rats. This was possibly the result of anticholinergic relaxation of the detrusor muscle, leading to the reflux of secretions from the accessory reproductive gland in the urinary bladder.

Reproductive toxicity studies were performed in rats and rabbits using oral and inhaled doses of tiotropium. In both species inhaled drugs were readily absorbed and absorption following oral dosing was poor. Reproductive toxicology studies showed no evidence of teratogenic effect in rats and rabbits at inhalation tiotropium doses of approximately 60 and 45 times the maximum recommended human daily dose (MRHD) in the respective species. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth, and a decrease in the mean pup weight were observed at inhalation doses approximately 3 times the MRHD. In rabbits, an increase in post implantation loss was observed at inhalation dose of approximately 45 times the MRHD. In fertility studies in rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of approximately 3 times the MRHD. No such effect was observed at approximately the MRHD. The fertility index, however, was not affected at inhalation doses of up to 60 times the MRHD. The sexual maturation in pups, as measured by vaginal opening in the female and occurrence of balanoprepuital skinfold in the male, was delayed by 1-3.5 days in pups exposed to the drug maternally. Based on these findings the pharmacology-toxicology reviewer is recommending a pregnancy category C for tiotropium and I concur with that recommendation.

Genetic toxicity and mutagenicity of tiotropium were studied in five assays and all were negative. The assays were bacterial gene mutation assay in vitro, V79 CHO cell mutagenesis assay in vitro, human lymphocyte chromosomal aberration assays in vitro, unscheduled DNA synthesis assay in the primary rat hepatocytes in vitro, and mouse micronucleus formation assay in vivo.

Carcinogenicity of tiotropium was assessed in three studies and all were negative. The carcinogenicity studies were a 104-week study in rats, a 83-week study in female mice, and a 101-week study in male mice. These studies were discussed at an Executive CAC Committee meeting on June 25, 2002. The Committee concluded that the studies were acceptable, each of the studies achieved the maximum tolerated dose of the drug based on the treatment-related increase in mortality in mice and decrease in body weight gain in rats, and tiotropium bromide produced no evidence of tumorigenicity in either species.

Clinical Pharmacology and Biopharmaceutics

It is important to note that during the drug development program, the formulation of tiotropium was changed a few times. The to-be-marketed formulation was used in phase 3 studies, which was different than the formulation used in the phase 2 studies. The phase 3 formulation contained a [redacted] which resulted in a decrease in particle size. A decrease in the particle size may result in more drug delivery to the lung. Thus a dose used in phase 2 studies likely delivered less drug to the lung as compared to the same nominal dose used in phase 3 studies. The delivery device was also changed from an earlier FO2 device called the Inhalator Inhelheim to the to-be-marketed HalndiHaler device. These formulation and device changes are relatively minor and not likely to impact the conclusions of the phase 2 clinical pharmacology studies.

Pharmacokinetic data for tiotropium were obtained from 15 clinical studies in approximately 600 patients. In addition, the applicant has conducted many in vitro studies to explore the metabolic pathways, stability, and protein binding characteristics of tiotropium. Office of Clinical Pharmacology and Biopharmaceutics (OCBP) reviewer Dr. Shinja Kim reviewed these studies in detail and has recommended that these studies provide adequate data to support the approval of Spiriva Inhalation Powder and I concur with that conclusion. The salient clinical pharmacology findings are summarized in the following paragraph.

The bioavailability of tiotropium is poor after oral administration, approximately 2-3%, and greater after oral inhalation, approximately 19.5%. The Cmax after oral inhalation occurred at 5 minutes, the time of the first sample. The drug remained measurable in the blood for 2-4 hours after single-dose oral inhalation. The volume of distribution is quite large, approximately 32 liters/kg. Approximately 74% of the drug is eliminated in the urine as the parent compound. Active renal secretion is likely, based on the observation that renal clearance of the drug exceeds the creatinine clearance. The fate of the remaining 26% of the dose has not been established, but it is probably metabolized by a combination of non-enzymatic hydrolysis and cytochrome P450 metabolism, predominantly CYP2D6 and to a lesser extent CYP3A4. Older patients and patients with impaired renal function exhibit increased plasma concentrations.

Clinical and Statistical

The clinical data submitted in support of this application are derived from studies performed as part of the BIPI's clinical development program of tiotropium. The applicant has not relied on reports in the medical literature or other sources of data. The clinical program submitted in support of efficacy and safety included six phase 3 pivotal studies and five supportive studies. Two pivotal phase 3 studies were conducted in US, were one-year in duration, and were placebo-controlled. Two phase 3 studies were conducted in Europe, were one-year in duration, and were active (ipratropium bromide MDI)-controlled. Two phase 3 studies were multinational, were six months in duration, and were placebo- and active (salmeterol xinafoate MDI)-controlled. The five supporting studies were conducted in the Unites States, United Kingdom, Japan, and Netherlands. They were primarily dose ranging studies.

The application was discussed at the PADAC meeting on September 6, 2002. The PADAC concluded that BIPI has demonstrated adequate safety of Spiriva Inhalation Powder in patients with COPD. The PADAC unanimously agreed that BIPI has submitted substantial and convincing evidence that Spiriva Inhalation Powder provides clinically meaningful bronchodilator effects in patient with COPD. However the PADAC also unanimously agreed that the applicant has failed to provide substantial and convincing evidence that Spiriva Inhalation Powder provides a clinically meaningful effect for the symptom of dyspnea in patients with COPD. Based on the PADAC recommendation, Dr. Sullivan has recommended an approval action on this application for the bronchodilation indication and not for the dyspnea indication and I concur with that recommendation. These clinical studies submitted to the NDA are reviewed in Dr.

Eugene Sullivan's excellent medical review. Only brief comments are made on some of the studies in the following paragraph.

A total of 4,124 subjects participated in the clinical program of tiotropium, of which 3,411 were COPD patients, of which 1,723 were exposed to tiotropium (powder capsule formulation). A total of 1,701 were exposed to the proposed marketed dose of 18 mcg. The safety database submitted to the NDA is sufficient to support approval. Adverse events related to anticholinergic effects such as dry mouth, urinary effects, and constipation were more common in the tiotropium treated patients. In the pivotal clinical trials there were subtle suggestions that tiotropium may be associated with adverse cardiac effects. Holter monitoring was done in one supporting phase 2 study. The adverse events will be adequately mentioned in the product label. The Holter monitoring safety data can be bolstered as post-approval study.

Various doses of tiotropium were investigated in several phase 2 studies. These studies were somewhat difficult to interpret because of several factors including differences in formulation and delivery devices used, differences in nominal doses used, and inadequate washout period. Nevertheless, the studies generally demonstrated dose-response in terms of efficacy and in terms of tolerability. Doses approximately 36 mcg were only modestly more effective than doses approximately 18 mcg, and were associated with greater incidence of dry mouth. The proposed dose of 18 mcg and the dosing interval of once a day is sufficiently supported by the limited phase 2 studies and pivotal phase 3 clinical studies.

The phase 3 trials for tiotropium have attempted to support both the efficacy of the drug as a bronchodilator, and the efficacy of the drug in the treatment of dyspnea associated with COPD. Each of the six trials have addressed the bronchodilator activity by assessing FEV1 measure as a primary or as a co-primary variable, and by secondary variables such as forced vital capacity, peak expiratory flow rates, and rescue albuterol use. The primary or co-primary variable was the change from baseline in the trough (pre-dose) FEV1 value. An advantage in using the trough FEV1 value is that it can provide support of the proposed dosing interval by demonstrating continued efficacy at the end of the dosing interval. Disadvantages in using the trough FEV1 value is that there is no consensus regarding the minimum magnitude of effect that can constitute a clinically meaningful effect, and efficacy is not determined during peak response where there is a general consensus that at least a 12% and 200 mL increase in FEV1 constitute a clinically meaningful bronchodilating effect. However, in some of the clinic visits serial spirometry were done, which allows for assessment of the peak response and durability of the response. In the two one year placebo-controlled US studies, the primary efficacy endpoint was trough FEV1 at 13 weeks. In both the studies, tiotropium was statistically superior to placebo on this endpoint with an effect size of 0.14 liters. Tiotropium was also statistically superior to placebo on this endpoint at all other clinic visits at weeks 1, 7, 25, 37, and 49 with mean effect sizes of 0.11 to 0.16 liters. The four other pivotal studies also showed statistically significant bronchodilator effect with similar effect sizes. The secondary efficacy variables were also generally supportive of bronchodilatory

efficacy. These data support that Spiriva Inhalation Powder provides statistically significant and clinically meaningful bronchodilation in patients with COPD.

The proposed dyspnea indication is based on assessment of the Mahler Transition Dyspnea Index (TDI). In four of the six phase 3 studies (the four one-year trials), TDI was assessed as a secondary efficacy variable, where the TDI data was analyzed using mean values. After noticing encouraging results in the TDI in the four phase 3 studies, BIPI decided to add TDI as a co-primary efficacy variable in the remaining two studies (the 6-month multinational placebo- and salmeterol-controlled studies). The protocols of these two studies were amended to include TDI as a co-primary variable after the studies were completed but before the blind was broken. This was discussed with the Division at a meeting prior to breaking the blind. The variable was assessed as focal TDI score at the end of the 6-month studies. The focal TDI score is the sum of the individual scores of the three components of the TDI – functional impairment component, magnitude of task component, and magnitude of effort component. In these two studies, the TDI analyses were based on responder analyses, where a threshold of 1 in the TDI was the definition of a responder. The primary endpoint was six months. The applicant's claim of the dyspnea indication is based primarily on these two 6-month studies. In both the studies, the percentage of responders was statistically greater in the tiotropium group compaed to the placbo group at six months. The percentage of responders in the tiotropium groups was 42% and 45% in the two studies, compared with 26% and 33% in the placebo groups. For comparison, the percentages of the responders in the salmeterol groups in the two studies were 35% and 48%.

Interpretation of the significance of the TDI data from these studies is also complicated because it is not clear that the TDI instrument is adequately validated for use in a drug-intervention study, and for use across various cultures and countries where the primary language is not English. Furthermore, it is clear that the instrument was not appropriately implemented in the clinical studies. These problems are captured in Dr. Sullivan's review and was also discussed at length at the PADAC meeting. Taking all these factors into consideration the PADAC concluded that BIPI did not provide convincing evidence to support the dyspnea claim for Spiriva, and I concur with that conclusion.

Data Quality and Integrity

The Division of Scientific Investigations (DSI) audited two study centers. These centers were selected because they enrolled a large number of patients and participated in the studies submitted to support the dyspnea indication. One center adhered to all pertinent federal regulations and good clinical investigation practices. The other center had one important protocol violation. At that center, the TDI questionnaire was improperly administered. Rather than having the investigator or a designee ask questions of the patients and complete the questionnaire, the patients themselves read the questionnaire and completed the form. The DSI recommended that data from this site not be used for efficacy conclusion. This further justifies the concerns on the validity of the method the TDI instrument was implement in various centers in the two studies.

All clinical studies were conducted in accordance with accepted ethical standards. No financial disclosure issues are present. BIPI submitted signed FDA Form 3454 for each of the six pivotal studies. The forms certify that BIPI did not enter into financial arrangements with any investigators whereby the outcome of the study could be affected.

Pulmonary-Advisory Committee Deliberation

The clinical issues pertinent to this NDA were discussed at a PADAC meeting held on September 6, 2002. The recommendations of the PADAC are discussed in above section. In summary, the PADAC unanimously voted in favor of Spiriva Inhalation Powder for the treatment of bronchospasm in patients with COPD, and unanimously voted against Spiriva Inhalation Powder for the treatment of dyspnea in COPD. The PADAC voted 8 to 3 in favor of the opinion that the safety database was adequate. Several members raised concerns that the database did not adequately represent patients other than the Caucasian race, and that patients with known cardiac disease, renal disease, or other diseases that can be adversely effected by known anticholinergic property of tiotropium were excluded. However, all were in agreement that such safety data could be obtained as post-approval studies.

Pediatric Consideration

This drug was developed for COPD. Because COPD is a disease of older adults, pediatric studies were not performed by BIPI. Pediatric studies for tiotropium are not necessary at this time because COPD does not occur in children.

Product Name

A proprietary name review consult was requested to the Division of Medication Errors and Technical Support (DMETS), Office of Drug Safety. On a consult review dated February 22, 2002, the DMETS raised no objection to the proprietary name Spiriva. The DMETS consult review also noted that Division of Drug Marketing, Advertising, and Communications (DDMAC) did not have concerns about the name with regard to promotional claims.

Labeling

BIPI has submitted product label, patient instruction for use, and carton and container label. BIPI had proposed indications for both bronchospasm and dyspnea in patients with COPD. As discussed above all reference to the dyspnea indiation will be removed form the label. Further, minor labeling changes will be negotiated with BIPI to adequately capture the clinical and other data in the product label.

Recommendation

Other than the CMC deficiencies identified above, BIPI has submitted adequate data to support the approval of Spiriva Inhalation Poweder for the treatment of bornchospasm in patients with COPD. Pending resolution of the CMC deficiency, this NDA is recommended an approvable action.

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/s/

Badrul Chowdhury
12/18/02 01:54:50 PM
MEDICAL OFFICER
Div Dir Memo

MEMORANDUM
Jan. 30, 2004

TO: File
FROM: Kenneth L. Hastings, Dr.P.H.

SUBJECT: NDA 21-395

I have reviewed the action package and the final label for Spiriva (tiotropium bromide inhalation) and concur that the application is approvable based on the pharmacology/toxicology data. The label is worded adequately. The post-marketing commitment by the Sponsor to qualify degradants is acceptable.

_____
Kenneth L. Hastings, Dr.P.H.
Associate Director for Pharmacology and Toxicology
Office of Drug Evaluation II

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/s/

Kenneth Hastings
1/30/04 02:51:57 PM
PHARMACOLOGIST

INTEROFFICE MEMO

TO: NDA 21-395, SPIRIVA (Boehringer Ingelheim)
FROM: Timothy J. McGovern, Ph.D., Supervisory Pharmacologist
DATE: January 7, 2004

This drug product is indicated for the long-term maintenance of bronchospasm and dyspnea associated with COPD. This application was originally considered to be approvable as per the Agency letter of December 20, 2002. From a nonclinical perspective, the sponsor adequately addressed the relevant toxicologic issues including chronic toxicity, reproductive toxicity, genetic toxicity and carcinogenicity and the application was recommended for approval pending adequate qualification of various drug product degradants and acceptable revisions to the product label (see initial NDA review by Dr. Luqi Pei dated September 20, 2002 and subsequent tertiary review by Dr. David Morse dated October 22, 2002).

From a nonclinical perspective, the resubmission of the NDA primarily dealt with product labeling revisions. Additionally, discussions were held with the sponsor regarding the drug product degradants and a 13-week rat study was submitted to the IND to support the qualification of the degradants. These issues were reviewed by Dr. Luqi Pei in a second NDA review and subsequent addendum (dated December 23, 2003 and January 7, 2004), an IND review (December 1, 2003) and a consult to the CMC review team (December 8, 2003). Overall, I concur with Dr. Pei's recommendation for approval.

In regard to the product label, a discrepancy exists between section 3 (Newly Suggested Labeling) and section 4 (Annotated Labeling) of Dr. Pei's review. The discrepancy relates to the last sentence of the first and third paragraphs of the "Carcinogenesis, Mutagenesis, Impairment of Fertility", the first paragraph of the of the "Pregnancy" section and the fourth paragraph of the "OVERDOSAGE" section. The text in section 4 is the recommended wording for this product. The text from section 3 was forwarded to the sponsor and incorporated into their revised label of December 30, 2003. The text should read as follows: "These dose multiples may be overestimated due to difficulties in measuring deposited doses in animal inhalation studies."

In regard to the degradant qualification issue, the sponsor provided inadequate nonclinical data to qualify the proposed drug product specifications. Dr. Pei reviewed a 13-week inhalation study in rats in which tiotropium was spiked with single degradants or with two degradants combined; of note, degradant was not included. It was concluded that the study provided an animal to human safety margin of only 1 to 1.5-fold (assuming 100% deposition in humans) for each tested degradant whereas a 10-fold safety margin is typically sought. This deficiency was discussed at a team meeting of January 7, 2004 and it was determined that this issue would not preclude approval of the application. This conclusion was based on an evaluation of the available the nonclinical data which, although dose ratios were not ideal, did not include serious toxicologic concerns, clinical experience with drug batches that included degradant levels approaching the proposed

specifications and extensive post-marketing experience outside of the United States. However, the sponsor should provide adequate nonclinical qualification data as recommended by Dr. Pei in his CMC consult for the individual degradants as a post-approval commitment. Alternatively, the sponsor could lower the current specifications for the degradant pairs to NMT 1% or develop methodology to identify the individual degradants and set the specifications for each at NMT 1%.

In conclusion, the application is recommended for approval pending incorporation of the above recommended revision to the product label. Further, the sponsor should agree to provide adequate nonclinical qualification data to support the proposed specifications as a post-marketing commitment or reduce the drug product specifications for the degradants that exceed the relevant ICH recommended levels.

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/s/

Timothy McGovern
1/7/04 02:15:50 PM
PHARMACOLOGIST

Memorandum

Date: 18 Oct. 2002

From: David E. Morse, Ph.D.
Assoc. Director (Pharm./Tox.), Office of Drug Evaluation II

To: Robert Meyer, M.D.
Director, Office of Drug Evaluation II

Cc: Badrul Chowdhury, M.D., Dir. (Acting), DPADP (HFD-570)
C. Joseph Sun, Ph.D., Sup. Pharm./Tox., DPADP (HFD-570)

Subject: NDA 21-395
SPIRIVA® Inhalation Powder (tiotropium bromide)
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-395, dated 12 Dec. 2001, Luqi Pei, Ph.D.
2. Pharm./Tox. TL Memoranda, dated 20 Sept. 2002, C. Joseph Sun, Ph.D.
3. Package Insert for SPIRIVA® Inhalation Powder, revision of 03 Dec. 2001

II. Background

The sponsor (Boehringer Ingelheim) is seeking approval of SPIRIVA® Inhalation Powder for the long-term maintenance treatment (once daily administration) of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema.[1] The co-administration (concurrent or sequential) of sympathomimetic bronchodilators, methylxanthines, and oral or inhaled steroids (commonly used in the treatment of bronchospasm and COPD), is expected, although such use was not specifically evaluated for safety and efficacy.[2] Based on the indolent nature of COPD, it should be expected that an extended period of exposure to SPIRIVA® is likely in those patients who achieve satisfactory clinical benefit.

Tiotropium bromide is a long acting muscarinic cholinergic receptor antagonist. It binds to all members of the muscarinic receptor family (i.e., m_1-m_5), but with somewhat greater affinity for the m_3-m_5 receptors subtypes (i.e., Kd = 9pM for the m_{3-5} receptors vs. a Kd of 32-151 pM for m_{1-2} receptors). Tiotropium bromide possesses long acting bronchodilating properties via stimulation of the m_3 receptors of the respiratory tree. It has been shown to

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[1] The product is indicated for use in the maintenance therapy of bronchospasm in COPD patients, and makes specific reference to contraindications for use (see Warnings section of label) in the treatment of acute episodes of bronchospasm (i.e., rescue therapy). No reference or warnings regarding the potential use of SPIRIVA® for bronchospastic disorders in non-COPD patients (i.e., asthmatics) are provided in the product label.

[2] It should be noted that the supporting toxicity studies were not conducted with concurrent or sequential administration of other commonly used anti-bronchospastic therapeutics (i.e., bronchodilators, steroids, etc.), and therefore may not fully define the scope of potential toxicities associated with tiotropium bromide. It is unclear whether the integrated safety analysis of the clinical trial data contains sufficient numbers of patients and/or events to adequately address potential drug interaction issues.

block acetylcholine-induced bronchospasm or bronchospastic collapse in anesthetized dogs, guinea pigs and rats.

III. Comments and Conclusions

1. A review of the action package for NDA 21-395, SPIRIVA® Inhalation Powder (tiotropium bromide), indicates that the product has been evaluated in multiple acute, sub-chronic and chronic repeat-dose toxicity studies (up to 12 months repeat dose inhalation studies in rats and dogs), reproductive toxicity studies (Segments I and III in rats, and Segment II teratology testing in rats and rabbits), genotoxicity studies (mutation, cytogenetic and DNA repair studies), and multiple 2-yr carcinogenicity studies (rat and mouse) for approval as a chronic use product. The application adequately characterizes the toxicity profile of inhaled tiotropium bromide to support approval for chronic use in the treatment of bronchospasm in COPD patients.

2. Review of the reproductive toxicity data for tiotropium bromide in rats, suggests a significant dose response related decrease in numbers of corpora lutea and implants, an increase in fetal resorptions, and an increase in the numbers of dead pups at birth. Further, it induced lower pup weights, increased numbers of litter losses and delayed sexual maturation in rats. Post-implantation losses were increased in rabbits. Tiotropium bromide administration (via inhalation or oral administration) did not cause any teratogenic effects in rats and rabbits. Delayed sexual maturation and post implantation losses were not observed in the oral embryo-fetal development studies in either species. Since these adverse reproductive effects were observed in the absence of significant maternal toxicity (or paternal toxicity when applicable), it is recommended that these study findings be included in the product labeling. The pregnancy section of the product label should be revised to reflect the adverse effects observed in animals treated with tiotropium bromide.

3. In an addendum to the NDA review, specific reference is made to several degradants (, found in the drug substance and/or finished drug product. It was the reviewer's conclusion that the submitted data did not adequately support the specification limits requested by the sponsor for the inclusion of the degradants in the drug substance and/or drug product. A clear resolution of this issue, either through additional testing or change in product specifications was not identified in the NDA action package. This issue needs to be addressed prior to product approval or as part of a post-marketing Phase IV agreement.

4. Review and revision of the proposed product labeling has been deferred based on the expected 'APPROVABLE' action for this application. However, it is recommended that in any future product labeling, consideration be given to the following comments:
   - It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, C_{max} or other relevant parameter) unless there is clear scientific justification for the use of another scaling method (i.e., allometric scaling or nominal dose), or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.
   - While interspecies dose comparisons may be performed based on body-surface-area adjusted doses, in accordance with Pharm./Tox. policy (PTCC Meeting of June 1999), the computed mg/m^2 dose for the animals should not be presented in the product label. Instead, the study description should include the administered dose (in units as defined in the toxicity study) and the relative interspecies dose comparison (e.g., Repro-

duction studies revealed evidence of impaired ovulation, increased pre-implantation loss and fetal resorptions in rats at doses ≥ 7 µg/kg/day; approx. 3 times the human dose on a body surface area basis.).

- Under the heading of "Carcinogenesis, Mutagenesis, Impairment of Fertility," the phrase " should be revised to read '
- The review indicates that GI absorption of tiotropium bromide following oral administration is very low, but does not specify an exact oral bioavailability in animals or humans. In order to avoid potential confusion regarding the positive findings in the inhalation reproductive toxicity studies and the lack of findings in the oral exposure reproduction studies, it is recommended that the oral exposure studies not be included in the product label. Similarly, it is recommended that oral dosing studies not be described in the "Overdosage" section of the product label.
- Under the heading of "Overdosage," it is suggested that the signs and symptoms noted in the high dose acute toxicity studies of tiotropium bromide inhalation or IV exposure be included, but that be eliminated from this section of the label.

IV. Summary

A review of the action package for NDA 21-395, SPIRIVA® Inhalation Powder (tiotropium bromide), indicates that the product has been evaluated in multiple acute through chronic toxicology studies (up to 12 months in two species), reproductive toxicity studies, genotoxicity and carcinogenicity studies for approval for long-term use in patients with COPD and bronchospastic airway disease.

There remains one outstanding issue that relates to degradants found in the drug substance and/or drug product. In an addendum to the NDA review, it was the reviewer's conclusion that the submitted data did not adequately support the specification limits requested by the sponsor for the inclusion of the degradants in the drug substance and/or drug product. A clear resolution of this issue, either through additional testing or a change in product specifications was not identified in the NDA action package. This issue needs to be addressed prior to product approval or as part of a post-marketing Phase IV agreement.

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/s/

David Morse
10/22/02 06:54:45 PM
PHARMACOLOGIST

INTEROFFICE MEMO

TO: NDA 21395
FROM: C. Joseph Sun, Ph. D.
SUBJECT: Team Leader NDA Review Memo
Date: September 20, 2002

I concur with the Pharmacologist's conclusion that the pharmacology and toxicology of tiotropium bromide have been adequately studied and that the drug is approval from a preclinical standpoint.

Tiotropium bromide is a muscarnic cholinergic receptor antagonist. It possesses long acting bronchodilating properties. It has been shown that it blocked acetylcholine-induced bronchospasms or bronchospastic collapse in anesthetized dogs, guinea pigs and rats.

Chronic inhalation studies up to 12 months were performed in rats and dogs. Target organs of toxicity were eyes, nose and salivary gland in both species, gastrointestinal (GI) tract, harderian gland , urinary bladder and pancreas in rats and heart and respiratory tree in dogs. Urinary bladder, GI tract, harderian gland and lung following IV (4 weeks) administration in rats and heart, eyes, salivary gland and GI tract following oral (13 weeks) administration in dogs were identified as target organs of toxicity.

Inhalation administration of tiotropium did not impair the fertility index in rats but produced low numbers of corpora lutea and implants, fetal resorption and dead pups at birth. It did not cause any teratogenic effects in rats and rabbits. However, it produced lower pup weights, litter loss and delay sexual maturation in rats and post implantation loss in rabbits. Delay sexual maturation and post implantation loss were not observed in the oral embryo-fetal development studies in both species.

Tiotropium was not genotoxic in five assays (Ames test, mammalian gene mutation assay in Chinese hamster ovary cells, chromosome aberration in human lymphocytes, unscheduled DNA synthesis in rat hepatocytes and in vivo mouse micronucleus test).

No evidence of tumorigenicity was observed in mice (101 weeks in males and 83 weeks in females by inhalation) and rats (104 weeks by inhalation).

With regard to labeling, carcinogenesis, mutagenesis and impairment of fertility and pregnancy category C sections on the package insert have been revised to incorporate the above-mentioned preclinical findings.

There is no outstanding preclinical issue.

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/s/

Joseph Sun
1/12/04 10:41:58 AM
PHARMACOLOGIST
Originally DFSed on 9/20/02.

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: February 22, 2002

IND NUMBER: 46,687

NAME OF DRUG: Spiriva (tiotropium bromide 18 mcg inhalation powder)
18 mcg capsules

IND HOLDER: Boehringer Ingelheim Pharmaceuticals, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Drug Products (HFD-570), for assessment of the tradename "Spiriva", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Spiriva is the proposed proprietary name for tiotropium bromide 18 mcg inhalation powder. Spiriva is indicated for the maintenance treatment of bronchospasm and dyspnea associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. Spiriva is a capsule containing 18 mcg tiotropium used in combination with the HandiHaler, a reusable inhalation device used to inhale the dry powder contained in the Spiriva capsule. For administration, a capsule is placed into the center chamber of the HandiHaler. The capsule is pierced by pressing and releasing the button on the side of the inhalation device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece. The recommended dosage of Spiriva is inhalation of the contents of one capsule, once daily, with the HandiHaler inhalation device. Spiriva will be supplied in cartons containing one HandiHaler device and blister cards [redacted] capsules per card) with a total of [redacted] 30, [redacted] Spiriva capsules. The use of Spiriva is contraindicated in patients with a hypersensitivity to atropine or its derivatives, i.e., ipratropium. As with other anticholinergic drugs, Spiriva should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or bladder-neck obstruction.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names that sound alike or look alike to "Spiriva" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system[4] (TESS) was conducted.
The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "Spiriva". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with Spiriva. Similarly, through independent review, one additional [redacted] was also determined to have sound-alike potential with the proposed name Spiriva. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

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[1] MICROMEDEX Healthcare Intranet Series, 2002, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2002).
[2] Facts and Comparisons, 2002, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, New Drug Approvals 98-02, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=searchss&state=3hec6f.1.1
[5] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Spiriva	Tiotropium bromide18 mcg inhalation powder, 18 mcg capsule	Inhalation of one capsule once daily with the HandiHaler inhalation device	
Certiva	Diptheria, tetanus toxoids, and acellular pertussis vaccine (7.5 mL)	Children: dose based on age and immunization schedule	S/A
Sporanox	Itraconazole, Capsule: 100 mg Oral solution: 100 mg/10 mL (150 mL) Injection Kit: 10 mg/mL (25 mL ampule), one 50 mL bag 0.9% NaCl, one filtered infusion set	Onchomycosis: Tablets: 200 mg once daily for 12 weeks Oral solution: 100-200 mg once daily IV: 200 mg twice a day for 4 doses, then 200 mg daily	L/A
			S/A

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three studies were conducted by DMETS and involved 113 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Spiriva with other drug names due to similarity in handwriting and verbal pronunciation of the name. Inpatient order and outpatient prescriptions were written, each consisting of marketed and unapproved drug products and a prescription for Spiriva (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretation and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

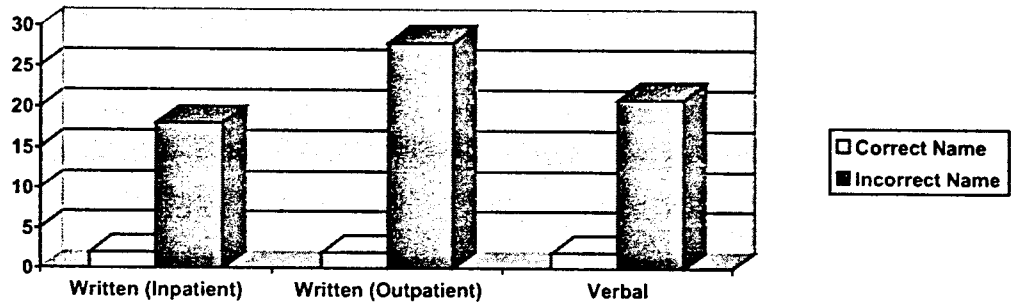
HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient RX: Spiriva one bid ud 30 day supply	Spiriva Take one tablet twice a day as directed. Dispense 30 with no refills.
Inpatient RX: Spiriva bid as directed by Hour Stage	

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted Spiriva	Incorrectly Interpreted
Written: Inpatient	34	20 (59%)	2 (10%)	18 (90%)
Outpatient	40	30 (75%)	2 (7%)	28 (93%)
Verbal: Outpatient	39	23 (59%)	2 (9%)	21 (91%)
Total	113	73 (65%)	6 (8%)	67 (92%)



Among the verbal outpatient Spiriva prescriptions, 21 of 23 (91%) respondents interpreted the name incorrectly. Many of the incorrect name interpretations were misspelled variations of "Spiriva". Incorrect interpretations included Spireva, Speriva, Sporida, Sprureva, Spreva, Scereva, Sperida, Spareva, Sporiva, Spariva, Sporeva, and Espiriva.

When examining the interpretations from the written inpatient prescriptions, 18 of 20 (90%) respondents interpreted the name incorrectly. Two of the incorrect responses were the marketed products Aspirin and Septra. Common incorrect responses were Spinver, Spinvir, Spinivir, Spinner, Spireva, Spinera, Spiniver, Spinvar, Spinvon, Spirivin, Spirivir, Spirum, Spirium, Spirever, and Spirirur.

In addition, 28 of 30 (93%) respondents from the written outpatient prescriptions interpreted the name incorrectly. Incorrect interpretations included Spikia, Spitiva, Spirae, Spirne, Spikir, Spitra, Spiria, Spiriv, and Spitac.

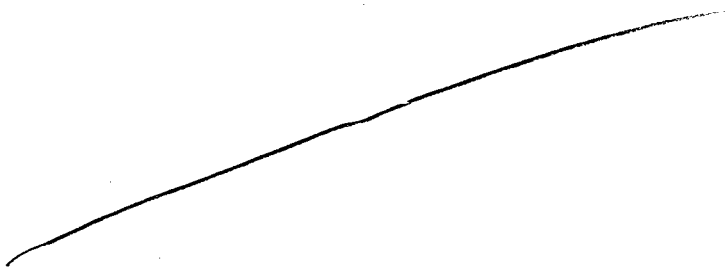
*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

C. SAFETY EVALUATOR RISK ASSESSMENT

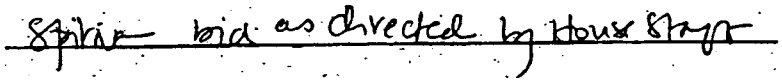
In reviewing the proprietary name "Spiriva", the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with Spiriva were Certiva and Sporanox. Similarly, through independent review, [redacted] was also determined to have sound-alike potential with the proposed name Spiriva. DMETS conducted prescription studies to simulate the prescription ordering process. *In this case, there was confirmation that Spiriva could be confused with Aspirin and Septra.* Two respondents from the written inpatient study interpreted the name to be Aspirin and Septra.

Certiva is a childhood vaccine used as the fourth and fifth dose in a primary immunization series against diptheria, tetanus, and pertussis from age 15 or 17 months through the seventh birthday. Certiva is available as an intramuscular injection that is stored by refrigeration. Although Certiva can sound-alike to Spiriva there are differences between the two that help to limit the risk for confusion. Both Certiva and Spiriva have different dosage forms (injection vs. capsule), routes of administration (IM vs. inhalation), patient populations (child vs. adult), and storage areas (refrigerator vs. room temperature). In addition, the Certiva injection is part of a child's immunization schedule and is often administered in doctors' office at specific, scheduled appointments thus adding another checkpoint for errors. Thus, due to the differences in dosage form, route of administration, patient population, storage, and drug administration the risk of a product mix-up between Certiva and Spiriva is minimal.

Sporanox (itraconazole) is an antifungal agent indicated in the treatment of onchomycosis of the toenail, as well as other susceptible fungal infections. Sporanox is supplied as 100 mg capsules, 100 mg/10 mL oral solution, and a 10 mg/mL injection kit. The recommended dose is 2 capsules (200 mg) given once daily for 12 weeks or 10 mL – 20 mL of the oral solution given once daily. The name Sporanox looks slightly similar to Spiriva. Each name contains the beginning stem "Sp" with no upstroke or downstroke letters to follow, and has three syllables. Yet, there are many factors that help to distinguish one drug product from the other. The two drugs have different strengths and indications for use. Spiriva is dosed as one inhalation (one capsule) once daily while Sporanox capsules are dosed as two capsules once daily. Similarly, the sig for Spiriva may often include the word "inhalation" which would help to distinguish it from the oral Sporanox. The risk of a product mix-up due to name confusion between Sporanox and Spiriva appears to be minimal.



One respondent from the written inpatient prescription study interpreted the name to be "aspirin". Aspirin (acetylsalicylic acid) and Spiriva can look similar when scripted in cursive. Below is the inpatient handwriting sample provided in the study.



However, a designating strength (81 mg, 325 mg, 500 mg) would most likely need to accompany or be verified for an aspirin prescription. Spiriva, on the other hand, is only available in one strength and does not require a designating strength to be prescribed. Aspirin is an over-the-counter drug product and Spiriva is only available by prescription. Aspirin and Spiriva would not be stored near each other in most pharmacies. Both drugs also differ in indication and dosage form (tablet/suppository vs. capsule) decreasing the risk of confusion between these two products.

One respondent from the written inpatient prescription study interpreted the name to be "Septra". Septra (sulfamethoxazole 400 mg and trimethoprim 80 mg) is a sulfonamide antibiotic used in

the treatment of urinary tract infections, acute exacerbations of chronic bronchitis, acute otitis media, traveler's diarrhea, and prophylaxis of *Pneumocystitis carinii*. Septra is available in tablets, oral solution, and intravenous injection. The usual recommended dose of Septra in adults with urinary tract infections is 2 tablets or four teaspoonfuls every twelve hours for ten to fourteen days. In addition, Septra is also available in a double strength formulation (sulfamethoxazole 800 mg and trimethoprim 160 mg) known as Septra DS. There are differences in dosing that help to limit confusion between the two drugs. Septra is normally dosed as two tablets or 4 teaspoonfuls twice a day while Spiriva is dosed as one inhalation once daily. In addition, Septra is most often prescribed for a short one or two-week regimen while Spiriva is a maintenance medication that needs to be taken daily to be effective. Septra and Spiriva have different indications for use, dosage forms, and dosing schedules limiting the risk for confusion and error.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Appropriate container labels, carton and insert labeling need to be reviewed when the NDA is submitted to the Agency.

IV. RECOMMENDATIONS:

DMETS has no objections to the use of the proprietary name, Spiriva.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names from this date forward.

Container labels, carton and insert labeling need to be submitted for review and comment when the NDA is submitted for review.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

_____

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

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

/s/

Nora L. Roselle
2/26/02 08:42:07 AM
CSO

Carol Holquist
2/27/02 06:50:50 AM
PHARMACIST

Jerry Phillips
2/28/02 11:24:39 AM
DIRECTOR

IMTS #5873

MEETING MINUTES

Meeting Date:	Monday, July 24, 2000
Meeting Time:	10:00-11:30 am
Meeting Place:	Conference Room "C"

IND #:	46,687
Sponsor:	Boehringer Ingelheim, Inc.
Drug:	tiotropium bromide inhalation powder
Indication:	dyspnea and bronchospasm associated with chronic bronchitis
Mechanism:	long-acting anti-cholinergic

Subject of Meeting: incorporation of dyspnea results into upcoming NDA

Meeting Participants

FDA:	Badrul Chowdhury	Team Leader, Clinical
	Ted Guo	Reviewer, Biometrics
	David Hilfiker	Project Manager
	Martin Himmel	Deputy Division Director
	David Hoberman	Reviewer, Biometrics
	Robert Meyer	Division Director
	Eugene Sullivan	Reviewer, Clinical
	Steve Wilson	Team Leader, Biometrics
BI:	P. Fernandes	Regulatory Affairs
	M. Kaplan	Regulatory Affairs
	S. Menjoge	Statistician
	C. Serby	Clinical Affairs
	T. Witek	Clinical Affairs

The sponsor stated that the focus for this meeting is to discuss dyspnea as a possible indication. At the last pre-NDA meeting (held on May 12, 1999), the sponsor presented four Phase 3 clinical studies, two which were conducted in Europe and two in the U.S. Dyspnea endpoints were not pre-specified in those four trials. The sponsor conducted two additional trials (Protocols 205.130 and 205.137) and pre-specified endpoints for dyspnea. The sponsor would like to use studies 130 and 137 as pivotal to supporting the dyspnea indication and the other four trials as supportive information.

The sponsor presented summary results of the change in transitional dyspnea index (TDI) focal score as the primary endpoint for dyspnea (see attachment 1 for slides).

FDA presented comments on the sponsor's questions presented on page 3 of the June 19, 2000. The sponsor's questions are provided in italics below. A summary of the discussion follows the question.

1. *Does the agency concur that the overall analysis and outcome for dyspnea observed in the four one-year Phase 3 studies are adequate to support the inclusion of dyspnea in the INDICATION AND USAGE section of the labeling?*

Dr. Sullivan stated that evaluation of the data will be part of the NDA review. In order to consider an indication for dyspnea, appropriate endpoints must be pre-specified in the pivotal studies.

2. *Does the agency concur that the overall analysis and outcome for dyspnea as observed in the four one-year Phase 3 studies are adequate (to) support the inclusion of dyspnea in the CLINICAL STUDIES section of the labeling?*

Dr. Sullivan stated that incorporation of the data from these studies into the CLINICAL STUDIES section of the labeling will be determined in the NDA review. He requested that the sponsor provide an analysis of each study separately as well as after combining the data, as the sponsor has indicated. Dr. Sullivan referred the sponsor to the Agency's comments on this topic at the May 12, 1999, pre-NDA meeting.

3. *Does the agency concur that the Studies 205.130 and 205.137 along with the proposed amendment is adequate to allow*

No. Salmeterol is not approved for dyspnea , and therefore is not an acceptable comparator.

ADDITIONAL DISCUSSION

Dr. Sullivan stated that the sponsor has defined a change of 1 in the TDI score (range is –9 to +9) to be a significant change, based on TDI developer Mahler's opinion. From a clinical standpoint, the significance of a change of 1 point is uncertain. As a composite score, an overall change of 1 could mean a positive change in one component that is masking a negative change in one or more of the other components. The sponsor should provide validation for this definition of a minimal meaningful change in the NDA.

Dr. Meyer added that the Division does not have experience with the TDI to accept on precedent a change of 1 point as clinically significant. Therefore, the sponsor will have to show that these changes in TDI are correlated to clinical improvement in the patients.

Dr. Sullivan noted that the sponsor has proposed excluding patients with an $FEV_1 > 50\%$ of predicted in the primary analysis of TDI. Dr. Sullivan stated that a primary analysis presented on a subset of patients may have ramifications for the labeling for dyspnea as an

indication. Dr. Himmel added that an initial study may identify a subset of patients who are better responders for the clinical endpoint through subset analyses of the data. Typically an additional study in the identified subset is necessary to demonstrate effects in the pre-specified population. Most indications are based on the analyses in the intent-to-treat population.

The sponsor asked if FDA could provide any comments on the proposed primary endpoint (change in TDI score) for dyspnea. Dr. Sullivan noted that a significant difference between groups (defined by the sponsor as a change of >1) was only seen on the last day of treatment. Dr. Sullivan also stated that the sponsor's responder analysis was not pre-specified.

The sponsor proposed combining the data from the four early Phase 3 studies and combining the data from 205.130 and 205.137 to furnish two data sets for the primary endpoints. FDA noted that dyspnea was not a primary endpoint in the first four studies that were conducted, and the combined analysis was not pre-specified in the data analysis plan for the NDA. Even if statistical issues regarding combining these studies (see below) could be acceptably addressed, the combined data would represent a single "study" in support of the dyspnea indication. Such a finding would then have to be replicated.

Dr. Guo asked the sponsor to provide their rationale for the stepwise approach proposed for the co-primary endpoints. The sponsor stated that with this approach they would not be required to adjust the Type 1 error. Dr. Guo noted that stepwise approaches are more common in the case of a single data set, but the sponsor is proposing to combine a number of data sets in the analyses. Dr. Guo suggested that the sponsor do a multiplicity comparison to adjust for the co-primary endpoints.

Dr. Himmel noted that dyspnea was not pre-specified as a primary endpoint in the four Phase 3 studies, and even with a combined approach, the sponsor has not replicated the results to support a dyspnea indication. Dr. Meyer added that the Division will not agree at this time that studies 205.130 and 205.137 are adequate to support approval of a dyspnea indication. Dr. Guo requested that the sponsor resubmit a statistical plan for the pivotal studies in the NDA once all pivotal studies have been identified.

Dr. Meyer referred to the sponsor's plans for

Dr. Meyer stated that data from subdomains within the St. Georges Respiratory Questionnaire (SGRQ) and SF36 instruments will not be considered as

Dr. Sullivan added that the sponsor will need to support the validity of subdomain results if there are plans to use individual subdomains in the NDA. The sponsor stated that they only planned

and these endpoints were pre-specified in studies 205.130 and 205.137.

The sponsor noted that frequency of exacerbations were significantly different between treatment groups and asked Dr. Meyer stated that it will be addressed in our review, and advised the sponsor to pre-specify this endpoint in any further studies used to support the NDA.

Dr. Meyer confirmed with the sponsor that the tradename used in the meeting package, SPIRIVA, may be forwarded for consideration by OPDRA as a proposed tradename.

Drafted by: HFD-570/Hilfiker/8-2-00
Final by: HFD-570/Hilfiker/8-14-00

Attachments: (1) BI presentation slides (11 pages, hard copy only)

Cc: Original IND 46,687
HFD-570/Div File
HFD-570/Hilfiker
HFD-570/Sullivan/8-4-00
HFD-570/Chowdhury/8-4-00
HFD-570/Guo/8-7-00
HFD-570/Wilson/8-7-00
HFD-570/Meyer/8-14-00

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INDUSTRY MEETING MINUTES

DATE:	May 12, 1999
TIME:	3:00 p.m.
PLACE:	Parklawn 3rd floor Conference Room "O"
MEETING TYPE:	Pre-NDA (General)
APPLICANT:	Boehringer Ingleheim Pharmaceuticals
IND/NDA:	IND 46,687
DRUG:	Tiotropium Powder Inhalation System
IMTS#:	

DIVISION OF PULMONARY DRUG PRODUCTS

Tien-Mien Chen, Ph.D., Clinical Pharmacology and Biopharmceutics Reviewer
Keary Dunn, Regulatory Project Manager
Ted Guo, Ph.D., Statistical Reviewer
John Jenkins, M.D., Acting Division Director
Joseph Sun, Ph.D., Pharmacology and Toxicology Team Leader
Anne Trontell, M.D., Clinical Reviewer
Ramana Uppoor, Ph.D., Clinical Pharmacology and Biopharmaceutics Team Leader
Mark Vogel, Ph.D., Pharmacology and Toxicology Reviewer and Acting Team Leader
Steve Wilson, Ph.D., Statistics Team Leader

BOEHRINGER INGELHEIM

Burkhard Blank, M.D, Head International Project Management
Joachim Coenen, Toxicology
Bernd Disse, BI Clinical Management
Rolf Doerr, Drug Regulatory Affiars
Peter Fernandez, M.Pharm., Drug Regulatory Affairs
Stefan Heinrichs, Ph.D., Project Leader
Marty Kaplan, Drug Regulatory Affairs
Theresa Maloney, Drug Regulatory Affairs
Shailendra Menjoge, Statistics
Chuck Serby, Clinical
Werner Thielmann, Project Management, R&D
Dietrick Tuerck, PK
Amy VanAndel, Clinical
Ted Witek, Clinical

Background

BIPI submitted a Pre-NDA briefing document to the Division dated March 15, 1999, received March 16, 1999, for review and comment. BIPI is developing Tiotropium DPI,

an anticholinergic bronchodilator, for use in patients with chronic obstructive pulmonary disease.

This Pre-NDA meeting was split into two separate meetings due to scheduling conflicts with BIPI. The CMC portion of the Pre-NDA meeting took place on Monday, May 10, 1999. The following meeting minutes address questions and issues arising from the review of the remainder of the briefing package. The meeting agenda addressed each question contained in the briefing package as follows.

CLINICAL SECTION

1. Does the Division agree with the format for presentation of data and tables in the ISS and ISE?

    1. **RESPONSE**: The table format for the ISS and ISE is acceptable. BI agreed to submit the final Year 1 Phase III study reports to the IND in these formats and remains open to suggestions. The Division commented that Graphs of FEV1 over 3 hours using letters for treatment days are difficult to read. At a minimum, 3 time points merit individual graphs (Day 1, Day 8, and Day 92)

2. At this time do you have any comments or recommendations regarding the strategy for presentation of the safety data in the ISS analysis plans (Clinical Section 4) or in the DRAFT labeling (Clinical Section 3)?

    RESPONSE: The proposed focus and presentation of the ISS are acceptable.

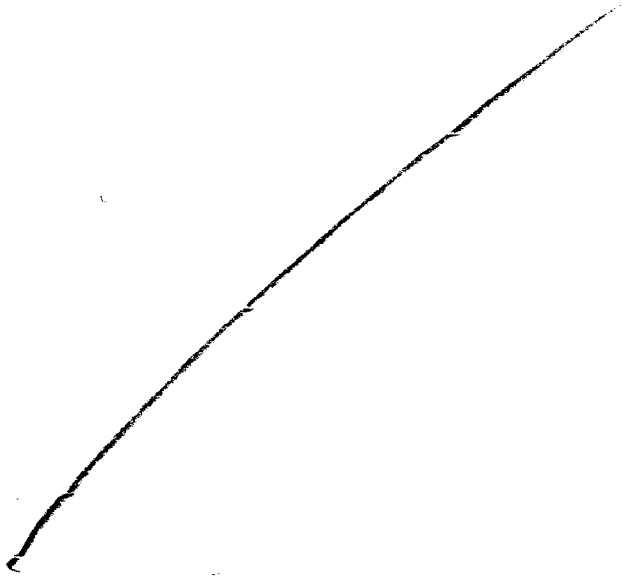
3. At this time do you have any comments or recommendations regarding the strategy for presentation of the efficacy data in the ISE analysis plans (Clinical Section 5) or in the DRAFT labeling (Clinical Section 3)?

    RESPONSE: The proposed focus and presentation of the ISE are acceptable.

4. The interim report for the first three-months will not be submitted separately in the NDA, as these data will be included in the full one-year reports. Does the Division agree with this approach?

    RESPONSE: The interim results from the 1-year studies do not need a separate submission. It was noted that in the EOP2 meeting with the Division, BI indicated that trough FEV1 at week 13 would be the primary endpoint. BI confirmed that the primary endpoint will remain unchanged and will be presented clearly in the study reports.

5. Does the Division agree with our rationale to support the proposed [redacted]



6. For the NDA submission, the plan is to provide the annotated draft package insert a two column format (Clinical Section 3). Is this format acceptable?

   RESPONSE: The two column format for the draft package insert is acceptable.

Additional Clinical Comments

7. A Waiver from the Pediatric Rule will be required.
8. If asthma is pursued as an indication, pediatric studies may be required.

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY SECTION

1. As previously discussed with the Agency and as further outlined under the radio labeled study section, does the FDA concur that no additional radiolabeled studies with tiotropium are required?

   OCPB Response: Concur.

2. Does the FDA agree that metabolism of tiotropium bromide serves as a very minor pathway of excretion of the drug, and that a structural elucidation of the theoretically possible 200-500 generated Phase I and Phase II metabolites is not necessary?

   OCPB Response:

   Agree, provided that the following issue is addressed:

   It is recommended that the major metabolite(s) of tiotropium be identified and the pharmacologic activities of the major metabolite(s) be determined in vitro.

3. Does the FDA agree that a liver insufficiency study is not necessary for tiotropium bromide taking into account the small dose of tiotropium, that the renal excretion of unchanged drug accounts for 70% of the dose and that metabolism seems to play a very minor role in tiotropium excretion?

   OCPB Response: Agree.

4. Does the FDA agree that drug-drug interaction studies on the basis of metabolism interactions are not necessary of tiotropium?

   OCPB Response: Agree.

5. Taking into account the small tiotropium inhaled dose and its wide safety margin, are there any particular comments or concerns FDA may have regarding potential drug-drug interactions?

   OCPB Response:

   Since the unchanged tiotropium is reportedly excreted renally via active secretion, it is recommended that in addition to the proposed PK study in renal insufficiency (page 192), the following issues be addressed in the PK section of the NDA and in the proposed labeling for possible drug-drug interactions of tiotropium with drugs, 1) which also undergo active excretion or 2) which may cause renal toxicity.

6. Based on the list of studies to be presented in this section and on their respective brief overview, does the FDA concur that adequate human pharmacokinetic studies have been conducted to support the filing of this NDA?

   OCPB Response:

   It is recommended that the following issues be addressed:

   a. Specificity of the LC-MS-MS assay method which is reported to be very sensitive with the limit of quantitation (LOQ) of [redacted] for plasma and urinary samples.

   b. The ratio of blood to plasma concentrations *in vitro*.

   c. Information on linkage between the FO2 device used in several human PK studies and the HandiHaler used in the clinical trials and some PK studies to interpret the results of those PK studies which used the FO2 device.
   NOTE: In the meeting, it was clarified that the linkage between the FO2 and HandiHaler devices meant the inter-study comparison of PK data to

show similarity and/or difference between the two devices not the in vitro performance data of the devices. No new bioequivalence-type PK study is required since the to-be-marketed product (HandiHaler) is used in clinical trials and several PK studies.

d. In addition to the PK data that will be submitted electronically in the sponsor-selected format , the sponsor was requested to submit electronic files of Item 6, PK study summary section, and individual study synopsis in WORD format as review aid if possible.

STATISTICAL SECTION

No specific questions, however we had the following comments.

1. The sponsor needs to establish a primary efficacy variable. This variable serves as the single most important indicator for efficacy among all supporting outcome variables.
2. If the baseline variable is used as a covariate, the sponsor needs to explain why and how it is defined.
3. In the event of missing observations on a patient, the sponsor needs to explain how the missing observations are handled.
4. The sample graphs showing both visit and treatment as legends do not produce desirable visual effects. Graphs showing serial visits should be displayed side-by-side using the same scales for horizontal and vertical axes. Each graph shows FEV1 vs. hour.
5. Electronic-data submission:
   - Include demographic variables in a SAS data set. Patient ID serves as the index variable for merging purpose.
   - Include efficacy variables in a SAS data set. The recommended order for the necessary variables are: Center($), Patient($), Visit ($ or N), Time (N), baseline_var(N), Efficacy_Var (N), and so on. ($: Character Variable;N: Numeric Variable)
   - All variables in the SAS data sets should be properly labeled. No variable should be left unexplained, unless it is self explanatory, such as race, sex.
   - If a variable is derived from other variables, the sponsor needs to provide the mathematical formula of derivation.
   - Use SAS formats catalog sparingly.
6. Carcinogenicity study data:
   - The most important data set is tumor.xpt and bodyweight data. For the format specifications, first, go to http://www.fda.gov/cder/guidance/index/htm – then to Electronic Submissions – then to the second document, Regulatory submissions in Electronic Format – New Drug Application (January, 1999) – then to Appendix 1.
   - A sample of electronic data can be downloaded. From http://www.fda.gov/cder/guidance/index – Sample of An Electronic New Drug Application Submission (posted 2/17/99).

7. The sponsor needs to compose a list of acronyms, especially those only known to the sponsor.

PHARMACOLOGY, TOXICOLOGY AND METOBOLISM SECTION

No specific questions, however we had the following comments.

Carcinogenicity Studies: The Carcinogenicity Assessment Committee (CAC) will still need to evaluate early termination in Mid and High dose groups of the mouse carcinogenicity study.

Impurities: 90-day studies are preferred for toxicological qualification of impurities in products with chronic indications. The 4-week inhalation study of [redacted] may suffice if both are [redacted]. Genotoxicity studies should be done with full strength impurity rather than parent drug "spiked" with impurity. These tests are used appropriately for hazard identification rather than risk assessment. All components in a mixture may not be adequately tested when dose is limited by toxicity of another component.

ELECTRONIC SUBMISSION SECTION

1. Do you concur with our approach of submitting NDA item 11 (CRTs) as CRF level datasets only in electronic archival copy?

   RESPONSE: Concur, as per guidance.

2. Do you concur with our approach of submitting NDA item 12 (CRFs only in electronic archival copy?

   RESPONSE: Concur, as per guidance.

3. Do you agree with the general philosophy of this electronic submission proposal which is to provide hypertext links and bookmarks from the table of contents for pdf documents and only limited hypertext links in the body of the pdf files?

   RESPONSE: The Division stated that as long as the minimum suggestions of the guidance were adhered to in relation to hypertext links, there would be no refuse-to file issues, however, more is better.

4. Do you concur with our approach to submit the core clinical study reports and selected appendices on paper I the Review Copy and the remainder of the Appendices electronically in the Archival Copy?

   RESPONSE: Concur, as per guidance. FDA requested that BI specify which appendices were not to be provided on paper copy, and BI indicated that they

would be submitting sample reports to the IND within a few months, and that they would work with the Division to provide what was necessary to facilitate review of the NDA.

5. Please confirm that Appendix 1 from the Guidance for Industry "Providing Regulatory Submissions in Electronic Format – NDAs" (January 1999) rather than the "Formats and Specifications for Submission of Animal Carcinogenicity Study Data" from the Division of Biometrics I, II, II, and IV (12 March 1997) represents the most current format/presentation for carcinogenicity data?

   RESPONSE: The January 1999 guidance represents current agency recommendations.

Following the discussion of the questions submitted in the briefing package it was agreed that BI would submit a revised table indicating which sections of the NDA would be submitted electronically as archive and which sections would be submitted electronically as reviewer aids. The Division agreed that we would continue to work with the BI to arrive at a mutually beneficial compromise.

cc:
HFD-570/Bertha
HFD-570/TMChen
HFD-570/Poochikian
HFD-570/Trontell
HFD-570/Uppoor
HFD-570/Vogel
HFD-570/ChenTM
HFD-870/Uppoor
HFD-870/Dunn

Initialed by:
Drafted by: Dunn/F/T:

C:\mydocuments\BIPI tiotropium PreNDA.CMC.doc
MINUTES

INDUSTRY MEETING MINUTES

DATE:	May 10, 1999
TIME:	9:30 a.m.
PLACE:	Parklawn 10B-45 Conference Room
MEETING TYPE:	Pre-NDA (CMC)
APPLICANT:	Boehringer Ingleheim Pharmaceuticals
IND/NDA:	IND 46,687
DRUG:	Tiotropium Powder Inhalation System
IMTS#:	3898

DIVISION OF PULMONARY DRUG PRODUCTS

Craig Bertha, Ph.D., Chemistry Reviewer
Keary Dunn, Regulatory Project Manager
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Burkhard Blank, M.D, Head International Project Management
Peter Fernandez, M.Pharm., Drug Regulatory Affairs
Stefan Heinrichs, Ph.D., Project Leader
Steve Horhota, Ph.D., Pharmaceutics
Scott McGraw, Ph.D., CMC Administrator
Manfred Reiffen,Ph.D., Head of Development Department
Andreas Schmidt, Ph.D., Chemistry-Regulatory Affairs
Werner Thielmann, Ph.D. CMC and Preclinical Project Manager
Bernd Walther, Ph.D., Analytics
Michael Walz, Ph.D., Pharmaceutics
Eileen Wyka, Technical Drug Regulatory Affairs

Background

BIPI submitted a Pre-NDA briefing document to the Division dated March 15, 1999, received March 16, 1999, for review and comment. BIPI is developing Tiotropium DPI, an anticholinergic bronchodilator, for use in patients with chronic obstructive pulmonary disease.

This Pre-NDA meeting was split into two separate meetings due to scheduling conflicts with BIPI. The Clinical/Pre-clinical portion of the Pre-NDA meeting will take place on Wednesday, May 12, 1999. The following meeting minutes address questions and issues arising from the review of the CMC portion of the briefing package. The meeting agenda addressed each question contained in the briefing package as follows.

CMC Reviewer Comments (Drug Substance):

1. As discussed in CMC section 2.2.2 the [redacted] materials are described in the literature and are commercially available. In addition, extensive testing is conducted on the [redacted] with regard to impurities content, as recommended in the FDA guidance, "Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances." We will in the NDA describe the synthesis of tiotropium bromide with these [redacted] Does the FDA concur with this strategy?

   RESPONSE: As part of the NDA submission, provide information on the synthesis and controls for [redacted] or provide Letters of Authorization to the appropriate DMF where indicated. In addition, it is stated in the briefing package that " [redacted] Demonstrate the absence of [redacted]

   BI indicated that they obtain [redacted] themselves by an [redacted] and this will be the only source used to prepare the [redacted] The [redacted] will be made by BI. In addition, BI indicated that a study report on the [redacted] of the drug substance (DS) will be included in the application.

2. Differences between the testing specification proposed for drug substance batches to be manufactured during the validation/market supply and those manufactured for phase III and the NDA stability were discussed in CMC Section 2.3.1 and the following comparison table. Does the FDA concur that the proposed testing specification is adequate for release of drug substance batches?

   RESPONSE: The listed testing parameters appear to be sufficient for controlling the Drug Substance, however specific acceptance criteria cannot be addressed at this time. In regard to degradants [redacted], it was noted in the briefing package that these degradants are quantified by Thin Layer Chromatography (TLC). BIPI responded that [redacted] was tried however, the individual degradants could not be resolved with this method. Therefore, BIPI decided that the specificity gained using the TLC quantification method was more relevant.

   Concurrence was reached that the melting point test for the drug substance will be retained. The test is simple and serves as a qualitative double check on purity and crystalline forms.

   Concurrence was reached that in the NDA submission a table indicating the comparative purity profiles of the drug substance used in the pre-clinical, clinical trial and NDA stability batches (drug substance with [redacted]

) will be provided and the most recent methods will be used so the profiles can be prepared head-to-head.

BI confirmed that the sieving analysis and associated acceptance criteria presented in the pre-meeting package for the DS was for control of the material.

Concurrence was reached that particle sizing method and specifications for the drug substance should control the whole profile. The material should have controls for foreign particulates and, depending upon the results of the study results, controls of the

Concurrence was reached that the application will identify the sites of and the operating parameters (e.g. Any changes in during development will be clearly indicated and batches identified. BI stated, in response to our query, that currently there is only one site and that a prior approval supplement would be submitted if additional sites were to be added later.

Provide justification of the absence of testing BI indicated that the application will include data demonstrating that the DS

Concurrence was reached that BI will either provide samples of the color reference solutions (e.g , or correlate color reference solutions to American Public Health Association (APHA) solutions at the time of NDA submission.

3. As described in CMC Section 2.3.2 BI proposes an acceptance limit of not more than of the impurity This impurity has been qualified by toxicology studies. In addition, clinical studies have been performed using drug substance containing up to Does the FDA concur with the approach to setting specification limits and toxicology qualification of this impurity?

RESPONSE: The Division stated that in addition to the consideration of the impurity level for qualification, the data will be reviewed for all batches for this impurity, the effects on the level of this impurity from the synthesis changes will be considered as well as manufacturing capability, in order to arrive at a suitable specification limit. In addition, comment on the acceptance limit of up to could only follow the review of all of the above mentioned material.

Discuss the quantification of with the Pharm/Tox team.

4. As discussed earlier in CMC Section 2.2.3, the synthesis of the — NDA batches utilized the — which was synthesized using — The — which will be used for validation/market supply will be synthesized from — As discussed in CMC Section 2.2.3, a stability study on the drug substance manufactured using — will be performed. It will be compared with stability studies using drug substance — We propose to submit the — accelerated data in the NDA. We seek FDA concurrence to this strategy for addressing the proposed change.

   RESPONSE: Concurrence was reached that — accelerated stability data would be sufficient for filing the NDA provided the — impurities identified in the process of synthesizing — as opposed to preparation from — are shown to be sufficiently removed from the drug substance, i.e., the purity profiles of DS prepared with — and the — would be the same. The agency expressed concern that the analytical methods used for determining the impurities in the DS would be able to detect the additional impurities or subsequent reaction products of these that were unique to the — BI stated that the NDA would include spiking studies demonstrating the ability of the methods to detect these if they were carried through the synthesis.

   In addition, it was agreed that a — time point be added for the — study.

5. We seek FDA concurrence that the proposed attributes listed in the stability protocol in CMC Section 2.4.1 are suitable for the upcoming stability studies described above.

   RESPONSE: Depending on the results of the studies addressing — a test (e.g., — may be needed to monitor for changes in — during the stability studies. BI acknowledged this possibility.

   Monitor for both individual and total related substance in the stability protocol.

   Submit stability data for both — drug substance including tests for the profile of the particle size. BI acknowledged that they have stability data on — DS and data to support a re-test period of — for the — DS.

CMC Reviewer Comments (Drug Product):

Unrelated Comment: Provide specifications for the Particle Size Distribution (PSD) for — that are supported by data and narrow enough to distinguish between different — available from — (supplier).

1. We seek FDA's concurrence that the manufacturing changes described in CMC Section 3.1.2 can be justified by the proposed in-vitro equivalence tests.

   RESPONSE: Based upon the information provided in the briefing package, the basic approach of using in-vitro test results should be able to provide data to justify and support the manufacturing changes.

   BI clarified the definition of ' ——— in relation to the drug product formulation appearance as DP that has formed in ———

   The "tentative specifications" are currently worded vaguely. Change to quantitative terminology relating to the ——— . BI indicated that they were currently having trouble

2. As discussed in CMC Section 3.2.2.1, does the FDA concur with our approach to set final shelf-life specifications for total degradation based on data from the NDA stability program but limited by the decomposition rate of about — seen in clinical trial batches of Phase III?

   RESPONSE: From a QC perspective the specification limit will be based on levels of related substances found in the various types of batches and manufacturing capability. The final decision will be data driven.

   The Division stated that drug product batches should be clearly identified by number so that a correlation can be made to the clinical studies that used these DP batches.

   The drug shelf life will be based upon stability data provided in relation to all the climatic conditions of the United States (not just climatic zones I and II).

   In reference to the data submitted on total degradation of the DP (p. 232 of the package) the division asked if BI expected that with the proposed — limit for total degradation would they expect the drug product to pass after ——— at 30°C/70%RH. BI indicated that some batches may be borderline. The Agency also noted that, from the total degradation data provided for (p. 232) DP batch 892471 had a distinctly higher rate of degradation than the other two batches (802472 and 802473). BI had no explanation for this difference in DP degradation rate but stated that the ——— batch were unique for DP batch 892471 and that the other two batches with a lower rate of degradation shared the same ——— batches. BI indicated that investigation into the cause of this discrepancy will continue.

Post Meeting Note: In terms of the substantial stability difference noted between batch 892471 and batches 802472 and 802473, once the investigation has determined the cause

of the difference, corrective action should be taken based on these findings and verified with additional stability data to support the upcoming application.

3. Does the FDA concur with the proposed approach for setting specifications for Delivered Dose as discussed in CMC Section 3.2.2.2?

   RESPONSE: See recent draft guidance for our approach to setting specifications. Also, a statistical approach for setting specifications may not always be the best because it takes away the incentive for reducing product variability.

   The mean data for — batches appear to be well within — for all, yet — is proposed. Set the specifications based on the data.

4. Does the FDA concur with the approach for stetting specifications for Aeroynamic Particle Size Distribution based on the proposed grouping as discussed in CMC Section 3.2.2.3?

   RESPONSE: Groupings will not be agreed upon prior to NDA submission because groupings are based upon submitted data, however, we would like to have CI data in terms of the amounts of DS on the individual plates and accessories. The concept of controlling the profile by plate/accessory groups (3-4) is what is usually done.

   In terms of the proposed ranges of least to most amount found on the proposed groupings, typical approved ranges for the amounts for various fine particle groupings for inhalation powders are about 1.5 fold. It was reemphasized by the Agency that this range was an example and should not be taken as policy.

   Increasing the number of capsules per group can be discussed prior to NDA submission.

   The Agency encouraged that BI study the aerodynamic PSD using the — with the newer plate groupings (i.e., with the — since it may give a more defined profile of the smaller particles. In addition it was stated that if this is done, it may be possible to "drop" plates (e.g., — off the bottom of the cascade impactor if no active is left there.

5. We seek FDA's concurrence on the list of test methods and sample size proposed in the specification table (CMC Section 3.2.1) for release and shelf-life of the 18µg tiotropium capsule.

   RESPONSE: Foreign particulate contamination method should also examine for

6. We seek FDA's feedback on our proposed specifications for key attributes: *Degradation, Delivered Dose and Aerodynamic PSD as listed in the table in CMC* Section 3.2.1 and as discussed in CMC Section 3.2.2.

   RESPONSE: It is premature at this time to discuss specific acceptance criteria without having reviewed all of the data.

7. We seek FDA's comment to our wish to drop the testing parameter concerning the —, except for the determination of foreign particles (CMC Section 3.2.2.5).

   RESPONSE: Keep this test and try to establish a qualitative method with an appropriate baseline for examination of gross changes in the formulation. The Agency recognizes that it may not be possible to have a quantitative method but with a trained analyst, changes could be noted so that the proper follow-up could occur.

8. We request FDA's comment on the ongoing NDA stability study protocol provided in CMC Section 3.3.1.

   RESPONSE: Monitor — regularly in stability batches. BI clarified that the determination of " — was for the capsules packaged in bulk containers.

   Perform — at least annually.

   Add a — ime point to the — testing.

   In addition to an — test for — examine capsule for — —. BI indicated that they are currently attempting to develop a quantitative test for — but that with the current variability seen in the results, setting acceptance criteria would be difficult. The Agency encouraged a quantitative approach to — determination and control.

   — (30°/70%RH) and — (accelerated) stability data will be sufficient for filing. The submission of — stability data should be submitted within 3-4 months following NDA filing.

CMC Reviewer Comments (Device):

Unrelated Comment: Provide authorization for DMF's for review for the pertinent CMC information for device and components. Provide acceptance specifications and tests for verification of supplier results for device and components.

1. Does the FDA agree that the procedure to prove the safety of the components of the *HandiHaler device as described in CMC Section 4.1.3 is* adequate?

   RESPONSE: Consult the draft Packaging guidance and the draft guidance for the CMC submission for MDIs and DPIs. In addition, consult the Pharm/Tox group when assessing safety qualification for components of the device.

CMC Reviewer Comments (Primary Packaging Material):

1. In addition to the routine quality control testing for the primary packaging material (listed in CMC Section 5.0), [redacted] is proposed. Does the FDA concur with this approach?

   RESPONSE: No. [redacted], for components of the device that contact the patient's mouth, formulation, or play a key role in the device performance should be controlled upon acceptance of these components. Refer to the recommendations contained in the recent draft guidance for the CMC submission for MDIs and DPIs on this issue.

CMC Reviewer Comments (Special Studies):

1. We seek FDA's comments and recommendations to the special studies as described in CMC Section 6.0.

   RESPONSE: This was not discussed in the meeting. The Division has the following Post Meeting Suggestions.

   Post Meeting Notes Regarding Facsimile of May 5, 1999:

   - *We recommend a study to test the effect of the drug product during use on the emitted dose and aerodynamic PSD.*

   - *With regard to the modified [redacted] Blister [redacted] In our opinion the potential effects on the [redacted] from such a change should be assessed through stability studies, i.e., [redacted] of comparative accelerated stability before and after the packaging change.*

   - *For the option B of the modified [redacted] with the proposal to use the different [redacted] adequate accelerated and long-term stability data should be generated and submitted with the application to assess the effects from this modification.*

- *For the [redacted] Blister [redacted] in addition to the qualification information and data needed (e.g., composition, [redacted], both accelerated and long-term stability data would be needed for drug product with this blister presentation in the upcoming application. Since the clinical product was stored in the [redacted], comparative stability data for the product in that packaging presentation would need to be included in the application as well.*

cc:
HFD-570/Bertha
HFD-570/Poochikian
HFD-570/Trontell
HFD-570/Vogel
HFD-570/Dunn

Initialed by:
Drafted by: Dunn/F/T:

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MINUTES

END-OF-PHASE 2 MEETING

Meeting Date: December 3, 1996
Time: 3:30pm - 5:00pm
Location: Conference Room B, Parklawn Bldg.

IND: #46,687 (Tiotropium Powder Inhalation System)
SPONSOR: Boehringer Ingelheim Pharmaceuticals, Inc. (BI)

Representing FDA:
Barbara Bono, M.S., Statistics Reviewer
Dale Conner, Pharm.D., Clinical Pharmacology and Biopharmaceutics Team Leader
John Gibbs, Ph.D., Acting Division Director, DNDC II
Brad Gillespie, Pharm.D., Clinical Pharmacology and Biopharmaceutics Reviewer
Peter Honig, M.D., Medical Team Leader
John Jenkins, M.D., Division Director
Betty Kuzmik, R.N., Project Manager
Lorrie Manasse, Contract Facilitor
Linda Ng, Ph.D., Chemistry Reviewer
Guirag Poochikian, Ph.D., Chemistry Team Leader
Brian Rogers, Ph.D., Chemistry Reviewer
Cathie Schumaker, Chief, Project Management Staff
Joe Sun, Ph.D., Pharmacologist Team Leader
Satish Tripathi, Ph.D., Pharmacologist Reviewer
Anne Trontell, M.D., Medical Reviewer
Steve Wilson, Ph.D., Statistics Team Leader

Representing Boehringer Ingelheim Pharmaceuticals, Inc.:
Rolf Doerr, Ph.D., Regulatory
Peter Fernandes, M. Pharm., Regulatory
Martin Kaplan, Regulatory
Michael Krueger, Ph.D., Analytical Sciences
Schailendra Menjoge, Ph.D., Biometrics
Karl Rominger, Biopharm
William Roth, Biopharm
Christian Schilling, M.D., Project Manager
Charles Serby, M.D., Medical
Gerhard Sluke, Ph.D., Pharmaceutics
Werner Thielmann, Ph.D., Research and Development
Doug Wilson, Clinical and Regulatory
Ted Witek, Dr.P.H., Medical

Background
Reference is made to the sponsor's October 16, 1996, request for an End-of-Phase 2 Meeting, the pre-meeting packages dated October 24, November 5 and 20, 1996, and our November 26 and December 4, 1996, faxes.

Chemistry

Refer to Attachment A and comment #23 on Attachment C. Attachment A is an outline of FDA comments that were presented by Dr. Ng at the meeting regarding recommendations for lactose, synthesis of the drug substance, specifications for the drug substance and drug product, the HandiHaler device, and the stability protocol.

Concerning specifications and test methods, BI presented the particle size and dose uniformity data. FDA stated that the particle size distribution should be well-defined and the delivery dose significantly amended.

In this regard, it was suggested that complete particle size distribution profile for the device from the mouthpiece to the filter be established at all time points in stability studies and submitted. At a later date, i.e., post-approval, after accumulation of data, appropriate groupings could be determined for routine testing. ——— specification and testing to evaluate the size, shape and texture of the particle and foreign particles ( ) should also be submitted.

Concern was expressed by Dr. Poochikian and confirmed by Dr. Jenkins that the proposed specification for the delivered (emitted) dose was wide. The range for the emitted/delivered dose should be similar to that of Combivent.

For the Phase 3 studies and the final formulation, BI stated that there will be no changes in the composition and no changes in the batches for NDA stability. The pharmaceutics will probably improve with blending and the color of the capsule may change from ——— to a color to be decided.

Preclinical

Dr. Tripathi told BI that they have conducted (per the End-of-Phase 2 package) or are planning to conduct (per the annual report 1995-1996) an adequate number of preclinical studies to support the proposed Phase 3 clinical studies and submission of an NDA.

In addition, he stated that analytical results on impurities/degradants should be provided in tabular form for all relevant batches of drug product used for clinical and safety testing. Qualification of impurities/degradation products may require further testing of these products for general toxicity as well as genotoxicity. (Refer to copy of overhead, Attachment B)

Biopharm

Refer to biopharm comments 20-22 from the fax dated November 26, 1996 (Attachment C).

The sponsor pointed out the difficulties of performing a single-dose, oral, radiolabel, mass balance study due to the small dose administered. In an attempt to describe the disposition of the drug, the sponsor is conducting an absolute bioavailability study. They are also currently conducting *in vitro* studies to more fully characterize the metabolic potential of the drug and are planning an *in vivo* renal impairment study. Lastly, the sponsor stated that they are currently re-evaluating their original plans to

Dr. Gillespie agreed with their position.

Clinical

Refer to clinical comments #1-12 from the fax. The discussion that follows each number below correspond to the comments/recommendations with the same number on the referred fax.

1. BI would prefer using Atrovent during the baseline period as it allows a broad spectrum of COPD patients to participate. If its use in patients was withdrawn during the baseline period, the sponsor feels that they would lose many potentially good study candidates. FDA acknowledged the drawbacks of an atrovent washout, but remains concerned that a high drop-out rate from the placebo group could occur and compromise study results.

2. BI realizes that they could unblind the study but by the time the blind was broken, it would be a year into the study. One half of the patients would be beyond the 6 month point and the other half would be beyond the 9 month point. BI feels that opening the blind would not be of any value; if anything, it would bias the investigator to drop the placebo group. FDA stated that this was only a recommendation. Not unblinding the study will make it more difficult for BI, but it is acceptable to FDA.

3. BI stated that, in reality, very few patients would be likely to receive increased doses of theophylline. If, in fact, they did, BI acknowledged that it would be important to restabilize the drug prior to pulmonary function testing. The likelihood of this being an issue, however, is slim. BI does not wish to restrict the physicians' ability to treat patients.

4. BI agreed to clarify the use of antibiotics in their protocol or in a letter.

5. BI stated that the primary endpoint, trough FEV_1, will be

assessed at 13 weeks. They will specify this in the protocol.

6. The sponsor does wish to make label claims for [redacted] They plan to change to the St. George's Respiratory Questionnaire and the SF 36 (physical symptoms) and look at the differences. FDA emphasized that the sponsor should demonstrate that the measurement instruments they use are validated for the disease condition being studied. It is also their responsibility to prove that the differences shown are clinically meaningful. In addition, the sponsor must specify in advance the domain(s) on which they expect the product to "win", and limit statistical analyses of significance to the same domain(s).

   Dr. Jenkins stated that it is unclear how FDA will approach the [redacted] at this time since they are relatively new. CDER is currently developing a guidance document on this issue. In the meantime, the likelihood of FDA allowing labeling for these endpoints is very uncertain.

7. BI maintained that, in their experience, patient recorded diaries were not helpful. They were difficult to record and interpret. Instead, they explained that they are planning to acquire daily information on the following: PEFRs 3 times/day electronically, which gives FEV_1, data, and compliance information; as needed albuterol use during 6 hour intervals; answers to an activities question (Were you able to perform most of your daily activities?), and a visit question (Did you have an unscheduled visit to your healthcare provider today?). In addition, at each 3 week visit, the investigator will review the patient's daily records, document answers to questions on energy/fatigue, adverse events, and symptom scores (scores of 1-3 with 1=absent and 3=severe) and provide a physician global evaluation.

   FDA strongly emphasized that adverse events and symptom scores need to be recorded in real-time by the patients themselves and should not be filtered by the investigator. Patient recorded diaries for at least the first 13 weeks of the study would make it a much better study. It should not be difficult for elderly patients to record on a 0-3 or 0-5 scale. An open-ended space can be provided in the diary for the recording of any unusual experiences or matters that need to be brought to the physician's attention.

8. BI does wish to pursue a label claim of [redacted] Because tiotropium