CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021747Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 21-747
Supporting document/s:	Sequence 0000
Applicant's letter date:	April 7, 2011
CDER stamp date:	April 11, 2011
Product:	Combivent Respimat Inhalation Spray
Indication:	COPD
Applicant:	Boehringer Ingelheim
Review Division:	Pulmonary, Allergy and Rheumatology
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.,
Project Manager:	Miranda Raggio

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 21-747 are owned by Boehringer Ingelheim or are data for which Boehringer Ingelheim has obtained a written right of reference. Any information or data necessary for approval of NDA 21-747 that Boehringer Ingelheim does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 21-747.

Reference ID: 2960629

1 Executive Summary

1.1 Introduction

The 11-APR-2011 resubmission (NDA 21-747) is the applicant's response to the Agency's Complete Response letter issued on August 7, 2009. The resubmission contained no additional, new nonclinical data. Dr. Luqi Pei completed a filing review of the resubmission on April 26, 2011. The only outstanding nonclinical issue of the resubmission is the labeling review.

The original application was filed in October 2008. The CR letter was issued because of deficiencies in the clinical and product quality disciplines. There was no deficiency in the nonclinical data. See the review completed by Dr. Luqi Pei on April 14, 2009 for the original nonclinical review of the application. The review recommended approval of the application from the nonclinical perspective.

The Division had reviewed the draft labeling of the application previously in the first review cycle. The 07-AUG-2009 CR letter contained the Division's labeling recommendations. Nonclinical sections of the labeling recommendations were based on a review completed by Dr. Luqi Pei July 1, 2009.

The resubmission contains a new version of the proposed draft labeling. This version contains minor edits to the labeling that Division recommended previously in the CR letter. Also, the Agency's policy on labeling format of nonclinical data has changed recently. Particularly, it was decided to omit descriptions of nonclinical data in the Overdosage section and to eliminate Section 13.2 – Animal Pharmacology and Toxicology: Reproductive Toxicity Studies. The applicant's edits and the Agency's policy change necessitate another labeling review.

1.2 Brief Discussion of Nonclinical Findings

Not applicable. No nonclinical data were submitted.

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective. Dr. Luqi Pei completed a nonclinical review of the original application on April 14, 2009. That review concluded that applicant has satisfied nonclinical requirements of the application and recommended approval of the application. The resubmission contained no nonclinical data. No new nonclinical issues have been identified since the previous review. The current review recommends approval of the application.

1.3.2 Additional Non Clinical Recommendations

None.

Reference ID: 2960629

1.3.3 Labeling

Text below is recommended for nonclinical sections (8.1, 10 and 13) of the Combivent Respimat labeling. See Labeling Review section (p 5) for discussions.

8.1 Pregnancy

Teratogenic Effect: Pregnancy Category C.

COMBIVENT RESPIMAT Inhalation Spray

There are no adequate and well-controlled studies of COMBIVENT RESPIMAT (ipratropium bromide and albuterol sulfate) Inhalation Spray, ipratropium bromide, or albuterol sulfate, in pregnant women. Animal reproduction studies have not been conducted with COMBIVENT RESPIMAT. However, albuterol sulfate has been shown to be teratogenic in mice and rabbits. COMBIVENT RESPIMAT Inhalation Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ipratropium bromide

Oral reproduction studies were performed in mice, rats, and rabbits at doses approximately 340, 68,000 and 17,000 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 at maternal doses in each species of 10 mg/kg/day, 1,000 mg/kg/day and 125 mg/kg/day, respectively). (b) (4)

These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. Embryo toxicity was observed as increased resorption in rats at oral doses approximately 6,100 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 90 mg/kg/day and above). This effect was not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration.

Albuterol

Albuterol has been shown to be teratogenic in mice and rabbits. A reproduction study in CD-1 mice given albuterol subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at approximately equivalent to the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 2.5 mg/kg/day) (b) (4) None was observed at less than the MRHDID in adults (on a mg/m basis at a maternal dose of 0.025 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg/day isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at approximately 1,100 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 50 mg/kg/day).

10 OVERDOSAGE

The effects of overdosage are expected to be related primarily to albuterol sulfate. Acute overdosage with ipratropium bromide by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. Manifestations of overdosage with albuterol may include anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute, and exaggeration of the pharmacologic effects listed in the Adverse Reactions section [*see Adverse Reactions (6)*]. As with all beta-adrenergic aerosol medications, cardiac arrest and even death may be associated with abuse. Dialysis is not appropriate treatment for overdosage of albuterol as an inhalation aerosol; the judicious use of a cardiovascular beta-receptor blocker, such as metoprolol tartrate may be indicated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ipratropium bromide

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day. (b) (4)

Results of various mutagenicity/clastogenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day (approximately 3400 times the MRHDID in adults on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg/day (approximately 34,000 times the MRHDID in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Albuterol

Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat at dietary doses of 2, 10, and 50 mg/kg/day (approximately 20, 110, and 560 times the MRHDID on a mg/m² basis). In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg/day (approximately 2800 times the MRHDID on a mg/m² basis) and a 99-week study in hamsters at oral doses up to 50 mg/kg/day (approximately 470 times the MRHDID on a mg/m² basis) revealed no evidence of tumorigenicity.

Studies with albuterol revealed no evidence of mutagenesis.

Reproduction studies in rats with albuterol sulfate revealed no evidence of impaired fertility.

Reference ID: 2960629

LABELING REVIEW

Nonclinical sections of the proposed labeling submitted on April 11, 2011 were generally acceptable; however, edits are necessary. Edits are made to ensure that the labeling of the to-be-marketed product reflects the Center's most current policy on product labeling.

The Division reviewed the draft labeling of the to-be-marketed product previously. See the nonclinical labeling review completed Dr. Luqi Pei on July 1, 2009. Dr. Pei's recommendation was conveyed to the applicant in the in the Complete Response letter issued August 7, 2009. The new proposal contained minor edits to the text recommended by the Division in the CR letter. Table 1 (below) presents the text of the Pregnancy Section of the Ipratropium as an example.

Table 1: Text of Pregnancy Section for Albuterol

07-AUG-2009 CR Letter	11-APR-2011 Resubmission
(b) (4)	

The format of the new labeling proposal was in compliance with the new labeling initiative: the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006). It included appropriate sections and headings such as Sections 8.1 (Pregnancy), 10 (Overdosage), 13 (Nonclinical Toxicology) and 13.1 (Carcinogenicity …) and 13.2 (animal reproductive toxicology). The new proposal did not change the content of the labeling information.

However, the Agency recently changed its policy on labeling format for nonclinical data. Particularly, it has decided to remove the description of nonclinical data in the Overdosage section and to eliminate Section 13.2 – Animal Pharmacology and Toxicology: Reproductive Toxicity Studies. These edits and policy changes necessitate another review.

All nonclinical data in support of the product labeling was based on the currently marketed Combivent HFA product (NDA 20-291). There is no new data warranting significant deviation of the labeling content between the currently marketed and the to-be-marketed product except for dose ratios.

PREGNANCY

Edits to the proposed text for Section 8.1 are recommended. The edits are necessitated by the recent policy change: returning all information about animal reproductive and developmental toxicity data to the Pregnancy section. Specifically, Section 8.1 will contain all the information present in both sections 8.1 and 13.2. This practically returns the labeling of the currently marketed Combivent product with the exception of dose ratios between the animals and humans. The following discussion uses the Pregnancy section of albuterol as an example. The labeling of the currently marketed Combivent (NDA 20-291, approved on April 11, 2011) states:

> "Albuterol has been shown to be teratogenic in mice and rabbits. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25, and 2.5 mg/kg) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (equivalent to the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). None was observed at 0.025 mg/kg (less than the maximum recommended daily inhalation dose in adults). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg (approximately 660 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis)."

(b) (4)

. The Division recommended the following for Section 8.1 in the August 7, 2009 CR letter:

(b) (4)

The applicant accepted the above recommendations in the 11-APR-2011 resubmission. However, the labeling of the to-be-marketed and currently marketed Combivent products should be harmonized except for the dose ratios between animals and humans. Changes in dose ratios are needed because the to-be-marketed product will have lower nominal doses of ipratropium and albuterol than the currently marketed product. The suggested labeling for Section 8.1 is as following:

8.1 Pregnancy

Teratogenic Effect: Pregnancy Category C.

COMBIVENT RESPIMAT Inhalation Spray

There are no adequate and well-controlled studies of COMBIVENT RESPIMAT (ipratropium bromide and albuterol sulfate) Inhalation Spray, ipratropium bromide, or albuterol sulfate, in pregnant women. Animal reproduction studies have not been conducted with COMBIVENT RESPIMAT. However, albuterol sulfate has been shown to be teratogenic in mice and rabbits. COMBIVENT RESPIMAT Inhalation Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ipratropium bromide

Oral reproduction studies were performed in mice, rats, and rabbits at doses approximately 340, 68,000 and 17,000 times, respectively, the maximum recommended human daily inhalation dose (MRHDID) in adults (on a mg/m^2 at maternal doses in each species of 10 mg/kg/day, 1,000 mg/kg/day and 125 mg/kg/day, respectively). [redacted] (b) (4) . These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. Embryo toxicity was observed as increased resorption in rats at oral doses approximately 6,100 times the MRHDID in adults (on a mg/m^2 basis at maternal doses of 90 mg/kg/day and above). This effect was not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration.

[redacted] (b) (4)

Albuterol

Albuterol has been shown to be teratogenic in mice and rabbits. A reproduction study in CD-1 mice given albuterol subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at approximately equivalent to the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 2.5 mg/kg/day) [redacted] (b) (4) None was observed at less than the MRHDID in adults (on a mg/m basis at a maternal dose of 0.025 mg/kg). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg/day isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis

in 7 of 19 (37%) fetuses at approximately 1,100 times the MRHDID in adults (on a mg/m^2 basis at a maternal dose of 50 mg/kg/day).

(b) (4)

OVERDOSAGE

Edits to the proposed text for Section 10 are recommended. The edits are necessitated by the recent policy change: removing the discussion of nonclinical data in the section. The following is suggested edit to the Overdosage section (10).

> The effects of overdosage are expected to be related primarily to albuterol sulfate. Acute overdosage with ipratropium bromide by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. (b) (4)
>
> Manifestations of overdosage with albuterol may include anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute, and exaggeration of the pharmacologic effects listed in the Adverse Reactions section [*see Adverse Reactions (6)*]. As with all beta-adrenergic aerosol medications, cardiac arrest and even death may be associated with abuse. Dialysis is not appropriate treatment for overdosage of albuterol as an inhalation aerosol; the judicious use of a cardiovascular beta-receptor blocker, such as metoprolol tartrate may be indicated.

NONCLINCAL TOXICOLOGY

Edits to the proposed text for Section 13 are recommended. The edits are to ensure that the Combivent products will have the identical labeling except for dose ratios. Using the ipratropium carcinogenicity data (Section 13.1) as an example, Table 2 (next page) presents texts of the currently product and the to-be-marketed products. The review recommends the retain CR letter recommendation.

Table 2: Carcinogenesis Section of Ipratropium Product Labels

Combivent HFA (N20-291)	Combivent Respimat (NDA 21-747)	
Approved on April 11, 2011	August 7, 2009 CR Letter	11-MAR-2011 Proposal
Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg. This dose corresponds in rats and mice to approximately 230 and 110 times the maximum recommended daily inhalation dose of ipratropium bromide in adults, respectively, on a mg/m^2 basis.	(b) (4) [redacted]	Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day (b) (4) [redacted]

The suggested editing for Section 13 Nonclinical Toxicology is as following:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ipratropium bromide

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day. (b) (4) [redacted]

Results of various mutagenicity/clastogenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test, and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day (approximately 3400 times the MRHDID in adults on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg/day (approximately 34,000 times the MRHDID in adults on a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Albuterol

Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a 2-year study in the rat at dietary doses of 2, 10, and 50 mg/kg/day (approximately 20, 110, and 560 times the MRHDID on a mg/m² basis). In another study this effect was blocked by the coadministration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg/day (approximately 2800 times the MRHDID on a mg/m² basis) and a 99-week study in

hamsters at oral doses up to 50 mg/kg/day (approximately 470 times the MRHDID on a mg/m² basis) revealed no evidence of tumorigenicity.

Studies with albuterol revealed no evidence of mutagenesis.

Reproduction studies in rats with albuterol sulfate revealed no evidence of impaired fertility.

(b) (4)

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/s/

LUQI PEI
06/14/2011

TIMOTHY W ROBISON
06/14/2011
I concur

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 21-747 **Applicant: Boehringer Ingelheim** **Stamp Date:** April 11, 2011

Drug Name: Combivent **NDA/BLA Type:** NDA Resubmission

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?			Not applicable. No nonclinical information was submitted because no nonclinical deficiencies were identified in the Complete Response action letter of August 7, 2009. See nonclinical review of the original application completed by Dr. Luqi Pei on April 14, 2009.
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?			Not applicable. See comments in Item 1.
3	Is the pharmacology/toxicology section legible so that substantive review can begin?			Not applicable. See comments in Item 1.
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?			Not applicable. See comments in Item 1.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).			Not applicable.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?			Not applicable.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?			Not applicable.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
8	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			Not applicable.
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m2 or comparative serum/plasma levels) and in accordance with 201.57?			Yes. The proposal labeling is in the PLR format and in general complies with the 07-AUG-09 CR action letter. Minor edits to the text of the label was proposed and should be reviewed later.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)			To be determined in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?	x		The drug is approved and currently marketed for the same route of the administration and same patient demographics.
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable.

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES._____

If the NDA/BLA is not fileable from the pharmacology/toxicology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

No review issues were identified.

Luqi Pei, Ph.D. April 26, 2011
Reviewing Pharmacologist Date

Timothy Robison, Ph.D. April 26, 2011
Team Leader Date

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/s/

LUQI PEI
05/04/2011

TIMOTHY W ROBISON
05/04/2011
I concur

INTEROFFICE MEMO

TO: NDA 21-747, Combivent Respimat Inhalation Spray (Boehringer Ingelheim, Inc.)
Sequence number/date/type of submission:
#000/October 9, 2008/original

FROM: Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor
Division of Pulmonary and Allergy Products

DATE: June 8, 2009

I concur with the Dr. Luqi Pei's recommendation in the pharmacology and toxicology chemistry consultation completed March 31, 2009, the general pharmacology and toxicology NDA review completed April 14, 2009, and the nonclinical labeling review completed May 28, 2009 for Combivent Respimat Inhalation Spray (ipratropium and albuterol combination product). This application was submitted as a proposal to replace the currently marketed Combivent Inhalation Solution, a CFC-containing product, with Combivent Respimat Inhalation Spray that lacks the CFC ingredient. For this NDA, there were no novel excipients that were in need of safety qualification. The sponsor submitted inhalation toxicology studies in rats (up to 2-weeks duration) and in dogs (up to 3-months duration) for assessment of albuterol- (b) (4) Additionally, a 13-week inhalation study of EDTA and benzalkonium chloride was tested in rats. There were no new safety concerns observed in these studies for albuterol, EDTA or benzalkonium chloride. As described in Dr. Pei's chemistry consult (March 31, 2009), there were no safety concerns about the level of drug impurities, leachables, extractables, particulate matter and volatile residues.

Based on these reviews, Dr. Pei recommends the approval of NDA 21-747 from the nonclinical perspective. Recommendations of edits to the proposed nonclinical labeling of the product (sections 8.1, 10, 13.1, and 13.2) were made in Dr. Pei's review dated May 28, 2009. The nonclinical labeling review provided recommendations to the labeling to conform to the Agency's Draft Guidance for Industry, "Labeling for Human Prescription Drug and Biological Products- Implementing the New Content and Format Requirements" (January 2006).

_____

Molly E. Shea, Ph.D.
Acting Pharmacology/Toxicology Supervisor

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/s/

Molly Shea
6/8/2009 09:31:33 AM
PHARMACOLOGIST

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-747**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**October 9, 2008**
PRODUCT:	**Combivent Respimat Inhalation Spray (Ipratropium bromide & albuterol sulfate)**
INTENDED CLINICAL POPULATION:	**COPD**
SPONSOR:	**Boehringer Ingelheim**
DOCUMENTS REVIEWED:	**Vol. 1, proposed labeling**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Molly Shea, Ph.D.**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Miranda Raggio**

Date of review submission to Division File System (DFS): May 28, 2009

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability
The application is recommended for approval, from a nonclinical pharmacology and toxicology standpoint, as recommended in the Pharmacology and Toxicology Review completed by Dr. Luqi Pei on April 14, 2009 in the NDA application.

B. Recommendation for nonclinical studies
None.

C. Recommendations on labeling
Edits were made to the nonclinical sections of the proposed labeling. The edits were made to conform to the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006). Format of the proposed labeling was generally in compliance with the above guidance. The proposed labeling also retained the content of the labeling of Combivent Inhalation Aerosols with the approval date of November 10, 2008, except for dose ratios between animals and humans. The proposed labeling also included sections and headings (e.g., Sections 8.1, 10, and 13.1) that were absent in the approved labeling. Text was rearranged accordingly. These revisions are generally acceptable. Edits to the proposed labeling and rationales for the edits can be found in the Labeling Review of the document (next page).

II. Summary of nonclinical findings

Not applicable. All nonclinical findings were reviewed and summarized in the original Pharmacology Toxicology Review by Dr. Luqi Pei on April 14, 2009. No new, additional information has been collected since the original review.

LABELING REVIEW

Edits to nonclinical sections of the proposed labeling were recommended. Major edits were creating a new heading (i.e., 13.2 – Animal Toxicology and Pharmacology) and rearranging text accordingly. These edits were made to ensure that newly approved labeling will conform to the Draft Guidance for Industry "Labeling for Human Prescription Drug and Biological Products – Implementing the New Content and Format Requirements" (January 2006).

The proposed labeling was generally in compliance with the new labeling initiative. It included appropriate sections and headings such as Sections 8.1 (Pregnancy), 10 (Overdosage), 13 (Nonclinical Toxicology) and 13.1 (Carcinogenicity …). It, however, lacked Section 13.2 – Animal Toxicology and Pharmacology. Section 13.2 was added in the suggested labeling. Proposed text of Sections 8.1 was moved to Section 13.2. New text was written for Section 8.1.

The text of the nonclinical sections of the proposed labeling of Combivent Respimat was identical to that of labeling of the marketed Combivent Inhalation Aerosols, except animal-to-human dose ratios. The dose-ratio revisions were appropriate and will be discussed later in the review. The Combivent Inhalation Aerosols labeling was approved on November 10, 2008 (NDA 20-291). The nonclinical sections of the Combivent Inhalation Aerosols labeling were reviewed by Dr. Timothy McGovern in a Pharmacology and Toxicology Review on January 24, 2008 (DFS date).

The dose ratios between animals and humans in the proposed labeling were acceptable. These ratios of the Combivent Respimat differ from that of Combivent Inhalation Aerosols. The differences resulted from changes in the maximum recommended clinical doses of ipratropium and albuterol between the Inhalation Aerosols and Respimat products. Specifically, the respective maximum daily dose of albuterol (base) and ipratropium bromide was 1,236 and 216 µg/day in Combivent Inhalation Aerosols and 600 and 120 µg/day in Combivent Respimat.

This review used the same approach to calculate animal-to-human dose ratios for Combivent Respimat as for Combivent Inhalation Aerosols. Calculations for Combivent Inhalation Aerosols can be found on a Pharmacology and Toxicology Review completed by Dr. Timothy McGovern on January 24, 2008 (DFS date). Specifically, dose ratios in Combivent Inhalation Solutions were calculated using the following parameters: 1,236-µg albuterol and 216-µg ipratropium per patient, respectively. The daily albuterol and ipratropium dose was calculated from the parameters: 103-µg albuterol free base and 18-µg ipratropium bromide salt per actuation released from the mouth piece of the device; the maximum recommended dose of not exceeding 12 actuations a day.

The maximum recommended clinical dose of albuterol and ipratropium from Combivent Respimat would be only about half of the Combivent Inhalation Aerosols. Each actuation of the device would release 20-µg ipratropium bromide (monohydrate) and 100-µg

albuterol (equivalent to 120-µg albuterol sulfate).[1] The maximum allowable dose of Combivent Respimat was 6 actuations/patient/day. Consequently, the maximum recommended daily dose in Combivent Respimat would be 600-µg albuterol and 120-µg ipratropium bromide (monohydrate) per patient, respectively.

The lower maximum recommended daily doses of albuterol and ipratropium bromide resulted in higher animal-to-human dose ratios for each active ingredient. The proposed labeling took this into consideration. The review confirmed the sponsor's calculations. Parameters used to calculate these dose ratios are provided in Appendix 1. See Suggested Labeling section for labeling edits.

SUGGESTED LABELING

The following text is the suggested edits to the proposed labeling submitted on October 9, 2008. Highlighted sections indicate edits to the proposed labeling. Underlines and strikeouts indicate addition and deletion respectively.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects:~~,~~ Pregnancy Category C.

COMBIVENT RESPIMAT Inhalation Spray

There are no adequate and well-controlled studies of COMBIVENT RESPIMAT (ipratropium bromide and albuterol sulfate) Inhalation Spray, ipratropium bromide or albuterol sulfate, in pregnant women. Animal reproduction studies have not been conducted with COMBIVENT RESPIMAT. However, albuterol sulfate has been shown to be teratogenic in mice. COMBIVENT RESPIMAT Inhalation Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Ipratropium bromide

(b) (4)

[1] Labeling of Combivent Respimat does not distinguish the amount of drug released from the valve or mouth piece. It simply states that each actuation releases 20-µg ipratropium bromide (monohydrate) and 100-µg albuterol (equivalent to 120-µg albuterol sulfate)

(b) (4)

Albuterol

Albuterol has been shown to be teratogenic in mice and rabbits (b) (4)

(b) (4)

10 OVERDOSAGE

The effects of overdosage are expected to be related primarily to albuterol sulfate. Acute overdosage with ipratropium bromide by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after aerosol or oral administration. (b) (4)

(b) (4) Manifestations of overdosage with albuterol may include anginal pain, hypertension, hypokalemia, tachycardia with rates up to 200 beats per minute and exaggeration of the pharmacologic effects listed in the Adverse Reactions section [*see Adverse Reactions (6)*]. As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse. Dialysis is not appropriate treatment for overdosage of albuterol as an inhalation aerosol; the judicious use of a cardiovascular beta-receptor blocker, such as metoprolol tartrate may be indicated.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Ipratropium bromide

Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg/day. (b) (4) Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg/day (approximately 3,400 times (b) (4) -MHRDID on a mg/m² basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg/day (approximately 34,000 times (b) (4) MHRDID a mg/m² basis), ipratropium bromide produced a decrease in the conception rate.

Albuterol

Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a two-year study in the rat at dietary doses of 2, 10 and 50 mg/kg/day (approximately 20, 110 and 560 times the (b) (4) MHRDID on a mg/m² basis). In another study this effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg/day (approximately 2,800 times (b) (4) MHRDID on a mg/m² basis) and a 99-week study in hamsters at oral doses up to 50 mg/kg/day (approximately 470 times (b) (4) MHRDID on a mg/m² basis) revealed no evidence of tumorigenicity. Studies with albuterol revealed no evidence of mutagenesis.

Reproduction studies in rats with albuterol sulfate revealed no evidence of impaired fertility.

(b) (4)

APPENDIX

Table 1. Animal-to-Human Dose Ratios for Ipratropium in Combivent Respimat Labeling

Section No.	Description	Species	ROA	mg/kg	Km	mg/m^2	Animal-to-Human Ratio [a] Calculated	Rounded to [b]
8.1	Pregnancy	mouse	PO	10	3	30	338	340
		rat	PO	90	6	540	6081	6,100
		Rat	PO	1000	6	6000	67568	68,000
		rabbit	PO	125	12	1500	16892	17,000
		rat	ih	1.5	6	9	101	100
		rabbit	ih	1.8	12	21.6	243	240
10	Overdosage	mouse	PO	1001	3	3003	33818	34,000
		rat	PO	1663	6	9978	112365	112,000
		dog	PO	400	20	8000	90090	90,000
13.1	Carcinoge-nicity	mouse	PO	6	3	18	203	200
		rat	PO	6	6	36	405	400
13.2	Reproductive toxicity	mouse	PO	10	3	30	338	340
		rat	PO	90	6	540	6081	6,100
		Rat	PO	1000	6	6000	67568	68,000
		rabbit	PO	125	12	1500	16892	17,000
		rat	ih	1.5	6	9	101	100
		rabbit	ih	1.8	12	21.6	243	240

a. Based on a human dose of 0.09 mg/kg/day (i.e., 0.12 mg/patient/day for a 50-kg patient). A conversion factor of 37 was used to derive the a surface area dose (0.12 mg/day ÷ 50 kg/patient x 37 = 0.09 mg/kg/day).

b. Rounded to the nearest 10s, 100s and 1000 for 3-, 4- and 5-digit numbers, respectively. These numbers are used in the newly suggested labeling.

Table 2. Animal-to- Human Dose Ratios for Albuterol in Combivent Respimat Labeling

Section No.	Description	Species	ROA	mg/kg	Km	mg/m^2	Animal-to-Human Ratio [a]	
							Calculated	Rounded to [b]
8.1	Pregnancy	Mouse	SC	0.25	3	0.75	2	2
		Mouse	SC	2.5	3	7.5	17	15
		Mouse	SC	0.025	3	0.075	0	< 1
		Rabbit	PO	50	12	600	1,351	1,400
10	Overdosage	Mouse	PO	2000 [c]	3	5000 [c]	11,261[d]	11,000 [d]
		Rat	PO	2000 [c]	6	10000 [c]	22,522[d]	22,000 [d]
13.1	Carcinoge-nicity	Rat	diet	2	6	12	27	25
		Rat	diet	10	6	60	135	140
		Rat	diet	50	6	300	676	680
		Mouse	diet	500	3	1500	3,78	3,400
		Hamster	PO	50	4	200	450	450
13.2	Reproductive toxicity	Mouse	SC	0.25	3	0.75	2	2
		Mouse	SC	2.5	3	7.5	17	15
		Mouse	SC	0.025	3	0.075	0	< 1
		Rabbit	PO	50	12	600	1,351	1,400

a. Based on a human dose of 0.44 mg/m^2/day (i.e., 0.6 mg/patient/day for a 50-kg patient). A conversion factor of 37 was used to derive the a surface area dose (0.60 mg/day ÷ 50 kg/patient x 37 = 0.44 mg/m^2/day).

b. Rounded to the nearest integer, 5s, 10s, 100s and 1000 for 1, 2-, 3-, 4- and 5-digit numbers, respectively. These numbers are used in the newly suggested labeling.

c. Albuterol sulfate dose. 1.20 mg albuterol sulfate = 1.0 mg albuterol base.

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

/s/

Luqi Pei
5/28/2009 09:02:05 AM
PHARMACOLOGIST

Molly Shea
5/28/2009 10:48:14 AM
PHARMACOLOGIST
I concur.

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	**21-747**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**October 9, 2008**
PRODUCT:	**Combivent Respimat Inhalation Spray (Ipratropium bromide & albuterol sulfate)**
INTENDED CLINICAL POPULATION:	**COPD**
SPONSOR:	**Boehringer Ingelheim**
DOCUMENTS REVIEWED:	**Vol. C1 – C17**
REVIEW DIVISION:	**Division of Pulmonary and Allergy Products**
PHARM/TOX REVIEWER:	**Luqi Pei, Ph.D.**
PHARM/TOX SUPERVISOR:	**Molly Shea, Ph.D., Acting Supervisor**
DIVISION DIRECTOR:	**Badrul Chowdhury, M.D., Ph.D.**
PROJECT MANAGER:	**Miranda Raggio**

Date of review submission to Division File System (DFS): April 14, 2009

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

Pending a labeling review, an approval of Combivent® Respimat® Inhalation Spray is recommended from the nonclinical perspective. The application proposed to market Combivent® Respimat® as a replacement of the currently marketed Combivent® Inhalation Solution, a CFC-containing product. Both are combination products of albuterol and ipratropium. The proposed Combivent® Respimat® Inhalation Spray drug product recommends lower doses of albuterol and ipratropium than that of the currently marketed product. The formulation of the to-be-marketed product contains no novel excipients and the concentrations of each excipient are within the range of that in other approved and marketed products. The available nonclinical data are considered supportive of the intended use of Combivent® Respimat® Inhalation Sprays.

B. Recommendation for nonclinical studies

None.

C. Recommendations on labeling

A labeling review will be completed at a later time when the clinical use information of Combivent Respimat is finalized.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

The submission contained no new, significant nonclinical information about active or inactive ingredients of the Combivent® Respimat® Inhalation Sprays. The application submitted inhalation toxicity studies of (b) (4) (an aqueous albuterol solution containing benzalkonium chloride as an excipient) up to 2 weeks in rats and 3 months in dogs. The application also submitted a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any new, significant information about any of the three compounds: albuterol, EDTA and benzalkonium chloride.

B. Pharmacologic activity

No new data were submitted.

C. Nonclinical safety issues relevant to clinical use

None.

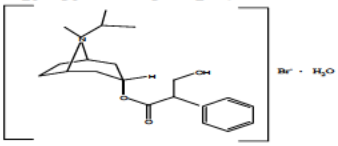
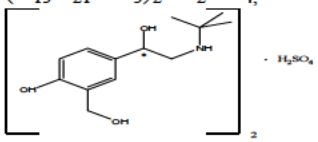
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA Number: 21-747
Review Number : 1
Sequence number/date/submission type: 000/ October 7, 2008/ N
Information to the Sponsor: Yes (x), No ( )
Sponsor/or Agent: Boehringer Ingelheim, Ridgefield, CT 06877
Manufacturer for Drug Substance: Boehringer Ingelheim, Ridgefield, CT 06877

Reviewer Name: Luqi Pei, Ph.D.
Division Name: Pulmonary and Allergy Products
Review Completion Date: April 14, 2009

Drug:

Trade Name:	Combivent® Respimat® Inhalation Spray	
Generic Name:	Ipratropium bromide	Albuterol sulfate
Code Name:	SCH 1000 BR	N/A
Chemical Name:	8-azoniabicyclo[3.2.1] octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-, bromide monohydrate, (3-endo, 8-syn)-	(1,3-benzenedimethanol, α'-[[(1,1dimethylethyl) amino] methyl]-4-hydroxy, sulfate (2:1)(salt)
CAS Register Number:	N/A	N/A
Molecular Form and Weight:	$C_{20}H_{30}BrNO_3 \bullet H_2O$; 430.4	$(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$; 576.7
Structure:		

Relevant IND/NDAs/DMFs: NDAs 20-691 (Combivent Aerosols)
INDs 57,948 (Combivent Respimat), (b) (4)

Drug Class: Bronchodilators (cholinergic and adrenergic antagonists)

Intended clinical population: COPD

Route of Administration: Oral inhalation

Clinical Formulation: Each actuation of Combivent® Respimat® inhaler delivers 20-µg ipratropium bromide (monohydrate) and 120-µg albuterol sulfate (100-µg albuterol base), (b) (4). The volume delivered from the mouthpiece is 11.4 µL. The EDTA and benzalkonium concentrations were (b) (4) respectively.

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

Studies reviewed within this submission:

Report #	Description	Vol.
U85-0169	Acute oral toxicity study of ipratropium in rats	1
U98-2224	2-week inhalation toxicity in rats with (b) (4) (b) (4)) formulation	1
U97-2076	2-week inhalation toxicity study in dogs with (b) (4) formulation	3
U97-2570	13-week inhalation toxicity study in the dog with (b) (4) formulation	3
U97-2343	Acute IV toxicity study of (b) (4) (albuterol degradant) in mice	4
U98-3066	Acute oral toxicity study in the mouse on (b) (4)	5
U05-1367	13-week inhalation toxicity study of Combivent plus (b) (4) in rats	5
U97-24l0	Ames test of (b) (4) and (b) (4)	6
U98-3010	Ames test of (b) (4)	6
U04-l247	Chromosomal aberration assay of (b) (4) in human peripheral blood lymphocytes	6
U06-1186	13-week inhalation toxicity study of disodium EDTA and benzalkonium chloride alone or in combination in water in rats	7

Studies not reviewed within this submission:

Report # [a]	Description	Vol.
U95-3057	Acute oral toxicity study in the mouse on (b) (4) and (b) (4)	5
U95-3056	Ames test of (b) (4)	6
U95-3l22	Ames test of Combivent inhalation solution in unit dose vials	6
U95-3119	Mouse lymphoma assay of (b) (4)	6
U95-3123	Mouse lymphoma assay of Combivent inhalation solution in unit dose vials	6
U95-3120	Chromosomal aberration assay of (b) (4) in human peripheral blood lymphocytes	6
U95-3121	Chinese hamster ovary cell forward mutation assay of (b) (4)	6
U95-3124	In vivo mouse micronucleus assay (b) (4)	7
U98-2727 [b]	(b) (4) 24 month inhalation carcinogenicity study in Wistar rats	8
U87-0028 [c]	(b) (4) chromosomal aberrations assay with human lymphocytes in-vitro	4
U86-0145 [c]	Micronucleus test of (b) (4)	4

a. These studies were not reviewed because they were either reviewed previously or provide no additional, significant value to the current review. The sponsor did not provide any information whether these reports have been submitted previously. A search of internal documents revealed that Dr. Mark Vogel reviewed all but Reports U87-0028, U86-0145 and U98-2727 on September 9, 1996 in IND 34,344.

b. Dr. Luqi Pei reviewed Study U98-2727 on September 17, 2002 in NDA 21-395.

c. It is unclear whether these two reports have been reviewed previously, but the current review does not evaluate them because they provide no additional value at the present time.

Drug History: This application (Combivent® Respimat® Inhalation Spray) is a reformulation product of Combivent® Inhalation Aerosol (NDA 20-291), a currently marketed drug product. Combivent® Inhalation Aerosol® is a CFC-containing product that is being phased out due to the environmental impact of CFC. The Combivent® CFC product was approved on October 24, 1996. The product was developed under IND 34,344. Once approved, Combivent® Respimat® will replace the Combivent® Inhalation Aerosol.

Combivent® Respimat® inhalation spray was developed under IND 57,948 which was filed originally on February 26, 1999. Several meetings with BI were held during the product development. Meetings dealing with nonclinical issues were the 20-FEB-1998 pre-IND meeting, the 10-MAY-2002 end-of-phase-2 (EOP2) meetings and the 30-SEP-2003 pre-NDA meeting. (b) (4)

(b) (4)

(b) (4)

The reports stated that the testing formulation was (b) (4) formulation. The reports, however, did not specify the formulation composition. It appeared that the testing formulation of the studies did not contain (b) (4). As alluded to later in the review, such information is not considered pivotal now since the Division considers that the safety of both excipients has been adequately established. Further, the above studies were not designed to evaluate the toxicity of the excipients.

The Division once expressed concerns about the presence of EDTA in the Respimat (b) (4). The concern was primarily about potential bronchospasm associated with the compound as reported in literature at the time (Beasley *et al.*, *Pharmacotherapy 1998;18:130-139*). The sponsor conducted a 13-week inhalation toxicity study of EDTA and benzalkonium chloride to address the concern. As indicted in the review, the study did not reveal any significant toxicity associated with the inhalation of the excipients.

The Beasley report prompted the Agency to conduct an internal evaluation of EDTA and benzalkonium chloride as excipients in inhalation products. The 20-FEB-1998 meeting was held during the early stage of the evaluation. The evaluation was completed in March 1999 when Dr. Luqi Pei filed a memorandum to Dr. Robert Osterberg, Chairman of the Inactive Ingredient Committee. The memo concluded that the safety of EDTA (b) (4) and benzalkonium chloride (b) (4)) in inhalation products had been established and no additional nonclinical data were needed for either compound.

The Division's position on the safety evaluation of the EDTA and benzalkonium chloride was reflected in the minutes of the 10-MAY-2002 EOP2 meeting. The minutes state: "The Division agreed that no additional toxicity studies are needed to support the Combivent Respimat NDA. The Division also reminded BIPI that we will evaluate the safety of degradants, extractables, leachables and impurities in the product during the review. Additional toxicity studies may be required if any of the above raise concerns."

The Division requested BI to evaluate the safety of degradants, extractable, leachables and impurities in the NDA submission in the EOP2 and the pre-NDA meetings.

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

No new data were submitted to this NDA. The labeling of the currently marketed Combivent states: "Combivent® (ipratropium bromide and albuterol sulfate) Inhalation Aerosol is expected to maximize the response to treatment in patients with chronic obstructive pulmonary disease (COPD) by reducing bronchospasm through two distinctly different mechanisms, anticholinergic (parasympatholytic) and sympathomimetic. Simultaneous administration of both an anticholinergic (ipratropium bromide) and a $beta_2$-sympathomimetic (albuterol sulfate) is designed to benefit the patient by producing a greater bronchodilator effect than when either drug is utilized alone at its recommended dosage."

2.6.2.2 Primary pharmacodynamics

Not applicable because no data were submitted.

2.6.2.3 Secondary pharmacodynamics

Not applicable because no data were submitted.

2.6.2.4 Safety pharmacology

Not applicable because no data were submitted.

2.6.2.5 Pharmacodynamic drug interactions

Not applicable because no data were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Not applicable because no data were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Not applicable because no data were submitted.

2.6.4.2 Methods of Analysis

Not applicable because no data were submitted.

2.6.4.3 Absorption

Not applicable because no data were submitted.

2.6.4.4 Distribution

Not applicable because no data were submitted.

2.6.4.5 Metabolism

Not applicable because no data were submitted.

2.6.4.6 Excretion

Not applicable because no data were submitted.

2.6.4.7 Pharmacokinetic drug interactions

Not applicable because no data were submitted.

2.6.4.8 Other Pharmacokinetic Studies

Not applicable because no data were submitted.

2.6.4.9 Discussion and Conclusions

Not applicable because no data were submitted.

2.6.4.10 Tables and figures to include comparative TK summary

Not applicable because no data were submitted.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Not applicable because no data were submitted.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Toxicity profiles of albuterol and ipratropium, alone or in combination, have been characterized previously. A pharmacology and toxicology review by Dr. C. Joseph Sun completed on November 9, 1993 in NDA 20-291 (Combivent Inhalation Aerosol) summarizes the then available toxicity data of albuterol, ipratropium and Combivent. All relative findings except for the general toxicity have been described in the currently marketed Combivent product. The target organs of toxicity were liver, GI tract, kidney, adrenal glands and reproductive organs (male) for ipratropium; and the heart, liver and testis for albuterol. Reference is made to Dr. Sun's review in NDA 20-291 for additional information. The following summary focuses on the new studies submitted in the current NDA application. Briefly, the studies did not reveal any new, significant findings.

Single-Dose Toxicity:

The oral median lethal dose (LD_{50}) of albuterol was 1,766 and 1,074 mg/kg in male and female rats, respectively. The minimum lethal dose was 1000 mg/kg.

Repeat-Dose Toxicity:

The application contained inhalation toxicity studies of albuterol (b) (4) formulation up to 2 weeks in rats and 3 months in dogs (Table 1).[1] These studies revealed that albuterol in the (b) (4) formulation possesses a toxicity profile typical of albuterol and other beta adrenergic agonists. The target organs of toxicity were the heart, liver and testis.

Table 1 Repeat-Dose Toxicity Studies

Test compounds	Studies	Report #
Albuterol	2-week dose-ranging IH toxicity in rats	U98-2224
((b) (4) formulation)	2-week dose-ranging IH toxicity study in dogs	U97-2076
	13-week IH toxicity study in dogs	U97-2570

In a 2-week rat dose-ranging inhalation study (U98-2224), Wistar rats (10/sex/dose) were given by nose-only inhalation albuterol up to 92 µg/kg/day for 14 days (achieved doses), and 1,328 µg/kg/day for one week. Rats were sacrificed 24 hours after the last exposure and pathological evaluations were carried out. No treatment-related effect was observed at any doses.

In a 2-week dog dose-ranging study (U97-2076), beagle dogs (1/sex/dose) were given by oral inhalation albuterol at 0, 17, (LD) or 121 µg/kg/day (MD) for 14 days (achieved doses), or 46 µg/kg/day for a week followed by 584 µg/kg/day (HD) for another week. Heart rate was measured after 1 minute, and 1 and 24 hours after the treatment in weeks 1 and 2. Dogs were sacrificed 24 hours after the last exposure and pathological evaluations were carried out. The albuterol treatment groups showed dose-dependent increases in heart rate and non-dose-dependent microscopic heart lesions. The mean heart rate at 1 hr after the treatment at week one was 78, 156, 165, 228 and 183 bpm and 17, 46, 121 and 584 µg/kg/day groups,

[1] The submitted toxicity study reports did not provide formulation composition information. They stated that the "Albuterol (b) (4) formulation" was tested. (b) (4)

respectively. The lower heart rate in the 584 µg/kg/day group was probably due to tolerance development for these dogs had been pretreated with 46 µg/kg/day albuterol for one week. The microscopic myocardial lesions were observed in all three albuterol-treated groups (one each). The lesion was described as necrosis combined with granulation tissue. The necrosis was "circumscribed, multifocal and distributed in the subendocardial layer".

In a 13-week inhalation study (U97-2570), beagle dogs (3/sex/dose) were given by nose-only inhalation albuterol 0 (vehicle), 42, (LD), 260 or 595 µg/kg/day (MD) for 13 weeks (achieved doses). The albuterol treatment groups showed dose-dependent increases in clinical signs, heart rate and in the incidence of cardiac lesions. Regarding the clinical signs, the mid- and high-dose groups showed dose-dependent increases in severity of reddening of skin, especially the earlobe, abdominal area and mucous membrane of the mouth. The respective mean heart rate at 1 hr after the treatment in the vehicle, LD, MD and HD groups was 68, 137, 147 and 158 bpm at week 1 and 65, 99, 95 and 100 bpm at week 13. Microscopic changes were limited to the heart, testis and liver in the MD and HD groups. The heart showed myocardial fibrosis in papillary muscle and left ventricle. The testis showed tubular degeneration and the liver showed fatty changes. The NOAEL appeared to be the low dose (42 µg/kg/day).

Genetic toxicity:

No new data were submitted. Neither albuterol nor ipratropium was genotoxic in *in vitro* and *in vivo* genetic toxicity assays. The labeling of the currently marketed Combivent Inhalation Aerosol states:

> "Results of various mutagenicity studies [with ipratropium] (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative." "Studies with albuterol revealed no evidence of mutagenesis."

Carcinogenicity:

No new data were submitted. Albuterol caused uterine leiomyomas in rats while ipratropium was non-carcinogenic in rats and mice. The labeling of the currently marketed Combivent Inhalation Aerosol states:

> "Two-year oral carcinogenicity studies [of ipratropium bromide] in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg. This dose corresponds in rats and mice to approximately 230 and 110 times the maximum recommended daily inhalation dose of ipratropium bromide in adults respectively, on a mg/m^2 basis."
>
> "Like other agents in its class, albuterol caused a significant dose-related increase in the incidence of benign leiomyomas of the mesovarium in a two-year study in the rat at dietary doses of 2, 10 and 50 mg/kg (approximately 15, 65 and 330 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). In another study this effect was blocked by the co-administration of propranolol. The relevance of these findings to humans is not known. An 18-month study in mice at dietary doses up to 500 mg/kg (approximately 1,600 times the maximum recommended daily inhalation dose on a mg/m^2 basis) and a 99-week study in hamsters at oral doses up to 50 mg/kg (approximately 220 times the maximum recommended daily inhalation dose on a mg/m^2 basis) revealed no evidence of tumorigenicity."

Reproductive toxicity:

No new data were submitted. Combivent Inhalation Aerosol, the currently marketed products, carries a Pregnancy Category C for its teratogenic effects. The labeling of Combivent Inhalation Aerosol states:

> "Ipratropium bromide: Teratogenic Effects:
>
> Oral reproduction studies were performed at doses of 10 mg/kg in mice, 1,000 mg/kg in rats and 125 mg/kg in rabbits. These doses correspond in each species, respectively, to approximately 190, 38,000, and 9,400 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg (approximately 55 and 140 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses 90 mg/kg and above in rats (approximately 3,400 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration.
>
> Albuterol Teratogenic Effects:
>
> Albuterol has been shown to be teratogenic in mice. A reproduction study in CD-1 mice given albuterol subcutaneously (0.025, 0.25 and 2.5 mg/kg) showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (equivalent to the maximum recommended daily inhalation dose on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). None was observed at 0.025 mg/kg (less than the maximum recommended daily inhalation dose in adults). Cleft palate also occurred in 22 of 72 (30.5%) fetuses treated with 2.5 mg/kg isoproterenol (positive control). A reproduction study with oral albuterol in Stride Dutch rabbits revealed cranioschisis in 7 of 19 (37%) fetuses at 50 mg/kg (approximately 660 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis)."

The above findings (except for the dose ratios) will be included in the labeling of the to-be-marketed product. Dose ratios will be revised according to expected changes in the recommended clinical dose.

Special Toxicity Studies:

Toxicity studies were completed to evaluate the general or genetic toxicity profile of excipients and drug impurities/degradants. The excipient study was a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. The degradant studies included general and genetic toxicity studies of albuterol degradants. Figure 1 (next page) presents the decomposition pathways of albuterol in an aqueous solution and chemical structures of several major degradants. The application submitted toxicity studies evaluating the genetic and general toxicity profiles of three degradants (impurities): (b) (4) ((b) (4) also code-named (b) (4) (b) (4) (b) (4) and (b) (4)

(b) (4)

Figure 1 Decomposition pathways of albuterol in aqueous solution.

Excipients:

Sprague-Dawley rats were exposed to aerosols containing (b) (4) EDTA and (b) (4) benzalkonium chloride alone or in combination for up to 20 minutes/day for 13 weeks. The estimated pulmonary deposition was 38.4 – 57.6 and 9.6 µg/kg/day for EDTA and benzalkonium chloride, respectively. Focal squamous metaplasia in the larynx and goblet cell hyperplasia in the nasal cavity were observed in rats treated with EDTA or benzalkonium chloride, alone or in combination. The findings were similar to what had already been known for these ingredients. There were no new, significant findings. The study did not reveal any NOAEL due to the presence of rat nasal findings.

Albuterol aldehyde

Several studies were completed to evaluate the genetic toxicity of albuterol. They include bacterial and mammalian cell gene mutation assays, mouse lymphoma assays, and a chromosomal aberration assay in peripheral human blood lymphocytes. The studies were reviewed previously by Dr. Mark Vogel on September 9, 1996 in IND 34,344. Briefly, albuterol aldehyde is genotoxic. Relevance of the findings had been considered previously in setting acceptable specifications in other products and will be repeated here.

(b) (4)

was evaluated for its genetic toxicity and general toxicity. The genetic toxicity studies of (b) (4) included 2 bacterial mutagenicity assays and a chromosomal aberration assay in human peripheral blood lymphocytes. (b) (4) tested negative in each assay. General toxicity of (b) (4) was evaluated in a 13-week inhalation toxicity study of

albuterol and ipratropium spiked with (b) (4) (b) (4) (relative to albuterol). Results showed that the addition of (b) (4) did not increase the toxicity of inhaled albuterol and ipratropium.

(b) (4)

was evaluated for its mutagenicity in the bacterial gene mutation assay. (b) (4) tested negative in the assay.

2.6.6.2 Single-dose toxicity

SCH 1000 BR hydrate (batch no. 406353): acute toxicity study after the oral administration to Chbb:THOM (SPF) rats; Vol. 1, Tab U85-0169

The median lethal dose (LD_{50}) of ipratropium after oral administration was determined in rats (Doc#U85-0169). Male and female rats [(Chbb:THOM (SPF), 5/sex] were given by oral gavage ipratropium in 0.1% Tween 80 (10 ml/kg) and were observed for up to 14 days post dosing. The respective ipratropium doses were 500 (female only), 1000, 2000, 3000 and 4000 mg/kg (male only). The respective incidence of deaths in the LD, MLD, MHD and HD group by day 14 post dosing was 0/5, 4/5, 5/5 and 5/5 in males and 0/5, 3/5, 5/5 and 5/5 in females. The minimum lethal dose was 2000 and 1000 mg/kg in males and females, respectively. The LD_{50} was estimated to be 1,766 and 1,074 mg/kg in males and females, respectively.

2.6.6.3 Repeat-dose toxicity

Study Title: 2-Week Inhalation (Nose/Mouth-Only) Range Finding Toxicity Study in the Rat on Albuterol (Salbutamol) (b) (4) Formulation

Key Study Finding: Wistar rats receiving by nose-only inhalation up to 1,328 µg/kg/day of albuterol (achieved dose) for 14 days did not show any significant toxicity.

Wistar rats [10/sex/dose, Chbb:THOM (SPF)] were exposed to 0 (air control, G1), 0 (vehicle control, G2), or albuterol in the (b) (4) formulation (G3 – 5, containing 0.02 – 3.0% albuterol) 30 minutes/day for up to 14 days. The mean achieved doses were 0, 0, 19, 45 (week 1) – 1,328 (week 2) and 92 µg/kg/day in Groups 1, 2, 3, 4 and 5, respectively. Macroscopic and microscopic examinations were done 24 hours after the last exposure. No remarkable abnormalities were observed in any of the treatment groups. The following information is for administrative purposes.

Study No.:	Doc. #U98-2224; Report#196003
Volume #, and page #:	Vol. 1, Tab U98-2224
Conducting laboratory and location:	(b) (4)

[2] The study reports also refer this compound as (b) (4)

	(b) (4)
Date of study initiation:	January 22, 1996
Report date:	February 20, 1998
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	Batch 241445; Purity: N/A

Study Title: 2-Week Inhalation (Mouth-Only) Range-Finding Toxicity Study in the Dog on Albuterol (Salbutamol) (b) (4) Formulation

Key Study Finding: Beagle dogs receiving by oral inhalation up to 584-µg/kg/day albuterol in a (b) (4) formulation for 14 days showed dose-dependent increases in heart rate and myocardial necrosis.

Beagle dogs (1/sex/dose) were exposed to air (G1), or (b) (4) vehicle (G2), or albuterol in (b) (4) formulation (G3 – 5) 10 - 75 minute/day for up to 14 days. The albuterol concentrations ranged 0.42 – 3.33%. The mean achieved doses were 0, 0, 17.4 and 121.2 µg/kg/day (G5) for the Groups 1, 2, 3 and 5, respectively. The albuterol dose in Group 4 was adjusted during the study as the previous dog study. Specifically, the achieved dose in Group 4 was 45.9 and 584 µg/kg/day for the periods of days 1-9 and 10-15, respectively. Macroscopic and microscopic examinations were done 24 hours after the last exposure.

Study No.:	Doc. #U97-2076; Report#152
Volume #, and page #:	Vol. 3, Tab U97-2076
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 15, 1995
Report date:	January 24, 1997
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	Batch 241445; Purity: N/A

Dogs in the albuterol treated groups showed dose-dependent increases in heart rate. Table 1 (below) presents the heart rate data. Note that the data were means from two dogs. Also, the respective albuterol dose in G3, G4 and G5 groups was 17.4, 45.9 and 121 µg/kg/day in week 1 and 17.4, 584 and 121 µg/kg/day at week 2. There was evidence of tolerance development in week 2. This was indicated by smaller degrees of heart rate increases in week 2 than week 1 at the same doses.

Table 2 Heart Rate in U97--2076

Group		WEEK -2	WEEK 1			WEEK 2		
			24 h	1 minute	1 h	24 h	1 minute	1 h
			AFTER ADMINISTRATION			AFTER ADMINISTRATION		
G1	MEAN	87	102	90	72	99	99	99
Air	DIFF		15	3	-15	12	12	12
Contr.	DIFF%		17	3	-17	14	14	14
G2	MEAN	99	84	84	78	72	84	72
Vehicle	DIFF		-15	-15	-21	-27	-15	-27
Contr.	DIFF%		-15	-15	-21	-27	-15	-27
G3	MEAN	105	105	141	156	84	132	135
	DIFF		0	36	51	-21	27	30
	DIFF%		0	34	49	-20	26	29
G4	MEAN	84	81	168	165	111	183	171
	DIFF		-3	84	81	27	99	87
	DIFF%		-4	100	96	32	118	104
G5	MEAN	96	120	231	228	96	165	174
	DIFF		24	135	132	0	69	78
	DIFF%		25	141	138	0	72	81

Dogs receiving albuterol treatment also showed microscopic heart lesions (incidence: one in each group). The lesion was described as necrosis combined with granulation tissue. The necrosis was "circumscribed, multifocal and distributed in the sub-endocardial layer".

Study Title: 13-Week Inhalation (Mouth-Only) Toxicity Study in the Dog on Albuterol (b) (4) Formulation

Key Findings: Beagle dogs receiving inhalation of 260 and 595 µg/kg/day of albuterol (achieved doses) showed dose-dependent increases in heart rate and microscopic lesions in the heart, liver and testis. Microscopic lesions in the heart included fibrosis in the papillary muscle and the left ventricle. Fatty changes were observed in the liver. The testis showed tubular degeneration (unilateral or bilateral). The NOAEL was 42 µg/kg/day.

Study No.:	Doc# U97-2570; Report# I96028
Volume #, and page #:	Vol.3, Tab U97-2570
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 28, 1996
Date of last treatment:	August 29, 1996
Report date:	October 21, 1998
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	260216 and 260221, purity 100.1%

Methods: Beagle dogs were exposed by oral inhalation to aerosols containing 0 (vehicle), 9.6, 58.7 and 96.8-µg albuterol per liter of air for 27 – 42 minutes/day for 13 weeks. The

vehicle was that of "Salbutamol (b) (4) formulation". Table 3 presents the dose estimate in the study. The achieved doses were calculated using the formula: Achieved (µg/kg/day) = [Albuterol concentration in test atomsphere (µg/L) x respiratory volume (l/min) x exposure time (min/day)] ÷ body weight (kg), where the respiratory volume was estimated by: RMV = 4.19 x body weight (g)$^{0.66}$. The MMAD ranged from (b) (4).

Table 3 Exposure Conditions and Dose Estimates of the 13-Week Dog Study

Group	Treatment	Study Period (week)	Exposure (minutes/day)	Albuterol in test solution (%)	Achieved inhaled dose (µg/kg/day)	Achieved inhaled dose (µg/kg/day)
1	Vehicle	1 – 6	27	-	0	0
		7 – 13	46	-	0	
2	Low dose	1 – 6	27	0.6	32.6	42
		7 – 13	27	0.84	48.5	
3	Mid dose	1 – 6	27	4.3	225.5	260
		7 – 13	27	6.55	286.7	
4	High dose	1 – 6	27	10.4	404.6	595
		7 – 13	46	10.4	743.9	

Doses: 42, 260 and 595 µg/kg/day (achieved doses)
Species/strain: Dogs, beagle
Number/sex/group (main study) or time point (main study): 3
Route, formulation, volume and infusion rate: Oral inhalation, 27 – 46 minutes/day, mean aerosol albuterol concentrations of 9.6, 58.7 and 96.8 µg/l air
Satellite groups used for recovery: None.
Age: 12 – 15 months
Weight (mean): 14.2 and 11.2 kg in males and females, respectively
Unique study design or methodology (if any) None.

Observations and Times:

Clinical signs: Daily
Body weights: Twice weekly
Food consumption: Weekly
Ophthalmoscopy: Pre-treatment and weeks 6, and 13
EKG: Weeks 1 and 13 at 1, 15, 60 minutes and 24 hours after treatment
Hematology: Pre-treatment and weeks 6, and 13
Clinical chemistry: Pre-treatment and weeks 6, and 13
Urinalysis: Pre-treatment and weeks 6, and 13
Gross pathology: Sacrifice
Organs weights: Adrenals, brain, gonads, heart, kidneys, liver, lungs, mandibular salivary glands, pituitary, prostate, spleen, thyroid glands
Histopathology: Control and HD groups: a complete panel for all groups;
Adequate Battery: yes (x), no ( )
Peer review: yes (x), no ( )
Other: Mass mean aerodynamic diameter (MMAD) was determined in weeks 1, 7 and 13 using an Anderson Mark 2 impactor.

Results

Mortality: No treatment-related effects were observed.

Clinical signs: The mid- and high-dose groups showed dose-dependent increases in severity of reddening of skin, especially the earlobe, abdominal area and mucous membrane of the mouth.

Body weights: No treatment-related effects were observed.

Food consumption: No treatment-related effects were observed.

Ophthalmoscopy: No treatment-related effects were observed.

EKG: The albuterol-treated dogs showed dose-dependent increases in heart rate, especially at 60 minutes post dosing. Table 4 presents the heart rate in Weeks 1 and 13. There was no prolongation of the QT-interval at any doses at either occasion.

Table 4 Heart Rate in the 13-Week Dog Study

		WEEK -1	WEEK 1				WEEK 13			
GROUP			1'	15'	60'	24 h	1'	15'	60'	24 h
1	MEAN	67.0	62.0	68.0	68.0	64.0	66.0	68.0	65.0	68.0
	DIFF		-5.0	1.0	1.0	-3.0	-1.0	1.0	-2.0	1.0
	DIFF %		-4	5	5	-1	3	5	0	6
2	MEAN	68.0	** 121.0	** 118.0	** 137.0	63.0	* 99.0	87.0	* 99.0	64.0
	DIFF		53.0	50.0	69.0	-5.0	31.0	19.0	31.0	-4.0
	DIFF %		83	80	109	-7	49	32	50	-4
3	MEAN	67.0	** 115.0	** 127.0	** 147.0	60.0	83.0	77.0	* 95.0	67.0
	DIFF		48.0	60.0	80.0	-7.0	16.0	10.0	28.0	0.0
	DIFF %		79	94	127	-6	30	22	51	4
4	MEAN	71.0	** 130.0	** 150.0	** 158.0	65.0	* 107.0	102.0	100.0	77.0
	DIFF		59.0	79.0	87.0	-6.0	36.0	31.0	29.0	6.0
	DIFF %		91	116	130	-5	55	49	46	11

Hematology: No treatment-related effects were observed.

Clinical Chemistry: No treatment-related effects were observed.

Gross pathology: No treatment-related effects were observed.

Organ Weights: No treatment-related effects were observed.

Histopathology: The mid- and high-dose groups showed dose-dependent increases in the incidence and severity of cardiac and testicular lesions (Table 5). The cardiac lesions included myocardial fibrosis in papillary muscles and left ventricle. The testis showed unilateral and bilateral tubular degeneration. The mid- and high-dose groups also showed more pronounced fatty changes. The low-dose group did not show any significant findings.

Table 5 Table Microscopic Findings in 13-Week Dog Study

Organ: observation	Severity	Male [a]				Female			
		G1	G2	G3	G4	G1	G2	G3	G4
Heart:fibrosis, subendocardial	Total	0	0	2	2	0	0	3	3
Papillary muscle, left	Mild			2	1				2
	Mild-mod.				1			2	1
	Mod.							1	
Mural, left ventricle	Mild							2	
Liver: Fatty changes	Total	3	3	3	3	3	3	3	3
	Very mild	2	3			1	3	3	3
	Mild	1	3	2	2			1	
	Mild-mod			1					2
	Mod				1			1	
	Mod-marked							1	1
Testis: tubular degeneration	Total	1	1	2	3				
Unilateral	Mild	1		2					
	Mod.				1				
Bilateral	Mild/mod.		1		1				
	Mod/remark.				1				

a. N = 3/dose in both males and females.

2.6.6.4 Genetic toxicology

Not applicable because no data were submitted.

2.6.6.5 Carcinogenicity

Not applicable because no data were submitted.

2.6.6.6 Reproductive and developmental toxicology

Not applicable because no data were submitted.

2.6.6.7 Local tolerance

Not applicable because no data were submitted.

2.6.6.8 Special toxicology studies

A 13-week rat inhalation study was completed to evaluate the effect of EDTA and benzalkonium chloride. A number of other studies were completed to evaluate the general and genetic toxicities of albuterol and ipratropium impurities/degradants: (b) (4) (b) (4) and (b) (4)

2.6.6.8.1 EDTA and Benzalkonium chloride Studies

Study Title: (Disodium EDTA) or (Benzalkonium chloride) or (Disodium EDTA + Benzalkonium chloride) in Acidified Demineralised Water: 13-week Inhalation Toxicity Study of Selected Vehicle Formulations in Rats

Key Study Finding: Inhalation of aerosols consisting of (b) (4) EDTA and (b) (4) benzalkonium chloride alone or in combination for up to 120 minutes/day resulted in focal squamous metaplasia in the larynx and goblet cell hyperplasia in rats. The combination treatment group showed a slight, but unremarkable increase in the severity of squamous metaplasia, compared to the individual treatment group.

Study No.:	U06-1186; Report#664458/23459
Volume #, and page #:	Vol. 7, page 1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 23, 2003
Report date:	January 27, 2006
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	N/A

Methods: Rats (Wistar Han IGS, 10/sex/group) were exposed by nose-only inhalation to aerosols consisting of (b) (4) benzalkonium chloride (BZK, Group 2) and (b) (4) disodium EDTA (Group 3), alone or in combination (Group 1), for up to 2 hours/day for 91 days. A water-only group (Group 4) from a contemporary 13-week study (b) (4) Project 664464) was used as a control. pH of each solution was (b) (4). Microscopic examination was done in a complete panel of organs and tissues in all groups.

Doses:	G4: 0 (vehicle, acidified water, pulmonary deposits) G1: 57.6-µg/kg/day EDTA + 9.6 µg/kg/day BZK (G1) G2: 38.4-µg/kg/day EDTA (G2) G3: 9.6-µg/kg/day BZK (G3) µg/kg/day
Species/strain:	Wistar Han IGS
Number/sex/group (main study) or time point (main study):	10
Route, formulation, volume and infusion rate:	Nose-only inhalation, up to 90 minutes/day; (b) (4) mg/ml EDTA and (b) (4) BZK alone or in combination
Satellite groups used for recovery:	None.
Age:	9 – 10 weeks
Weight (mean):	M: 145 - 187g; F: 116 - 156 g
Unique study design or methodology (if any)	Nose-only inhalation, 2 hours/day; Control group was from a contemporaneous study.

Observations and Times:

Clinical signs:	Daily
Body weights:	Twice weekly
Food consumption:	Weekly

Ophthalmoscopy:	Pre-treatment and week 4
EKG:	Not assessed
Hematology:	Week 7 and Sacrifice
Clinical chemistry:	Week 7 and Sacrifice
Urinalysis:	Not done
Gross pathology:	Sacrifice
Organs weights:	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus
Histopathology:	Control and HD groups: a complete panel for all groups; Adequate Battery: yes (x), no ( ) Peer review: yes (x), no ( )
Other:	Chamber EDTA and BZK concentrations were determined weekly from spare exposure ports. Samples collected from these ports were analyzed by HPLC. Particle size distribution was measured in once/week using a 7-stage cascade impactor.

Results

Dose estimates: The estimated pulmonary deposits were approximately 58-µg/kg/day EDTA and 10-µg/kg/day BZK in Group 1, 38-µg/kg/day EDTA only in Group 2, and 10-µg/kg/day BZK only in Group 3, respectively. Table 6 presents chamber aerosol concentrations of EDTA and BZK and dose estimates.

Table 6 Exposure Characteristics of EDTA and BZK Study

Group	Chemical	Concentration (µg/L)	MMAD	Inhaled Dose (µg/kg) [a]	Pulmonary [c] (µg/kg)
1	EDTA	6 ± 2	(b) (4)	576	57.6
	BZK	1 ± 0		96	9.6
2	EDTA	4 ± 2		384	38.4
3	BZK	1 ± 0		96	9.6
4	Water [c]	-		-	-

a. Derived from formula: inhaled dose = concentration (µg/L) x 0.8 L/min/kg x 120 min. The report did not provide estimates of total daily exposure.
b. Derived as the 1/10th of inhaled dose.
c. Shared group from contemporaneous study; not quantified for EDTA or BZK.

Mortality: One Group 3 (b) (4) BZK only) male died on day 29. No cause of death was identified.

Clinical signs: No treatment-related effects were observed.

Body weights: No treatment-related effects were observed.

Food consumption: No treatment-related effects were observed.

Ophthalmoscopy: No treatment-related effects were observed.

Hematology: No treatment-related effects were observed.

Clinical Chemistry: No treatment-related effects were observed.

Gross pathology: No treatment-related effects were observed.

Organ Weights: No treatment-related effects were observed.

Histopathology: The treatment of EDTA (G2) and BZK (G3) alone or in combination (G1) caused changes in the larynx and nasal cavity. The larynx showed focal squamous metaplasia. The nasal cavity showed goblet cell hyperplasia. Table 7 (below) summarizes the incidence and severity of the lesions.

Table 7 Table Microscopic Findings in Rats

Organ: observation	Severity`	Male				Female			
		G1[a]	G2	G3	G4	G1`	G2	G3	G4
Larynx: laryngeal focal squamous metaplasia	Minimal	0	4	5	0	0	5	2	0
	Mild	2	4	3	0	6	3	7	0
	Moder.	8	0	2	0	4	0	1	0
Nasal cavity: Goblet cell hyperplasia – Level I		4	1	8	0	3	0	3	0

a. Treatments were EDTA + BZK, EDTA, BZK and vehicle (water only) for G1, G2, G3 and G4, respectively.

2.6.6.8.2 [redacted] (b) (4) Studies

Study Title: [redacted] (b) (4) (Degradation product of Salbutamol) Acute Intravenous Toxicity Study in Mice

The median lethal dose (LD_{50}) of [redacted] (b) (4) after intravenous administration was determined in mice. Albino mice [Ico:OF(IOPS), 5/sex/dose) were given by intravenous injection 5 or 10 mg/kg [redacted] (b) (4) in saline (10 ml/kg, 0.1 ml/sec) and were observed for up to 14 days post dosing. All 10-mg/kg mice died; all deaths occurred within minutes post dosing. No deaths occurred in the 5 mg/kg/ group. Clinical signs included sternal recumbency, dyspnea, exophthalmia and tonic convulsion. The LD_{50} was estimated to be 7.4 mg/kg in both sexes. The following information is for administrative purpose.

Study No.:	Doc. #U97-2343; Study No. I97012
Volume #, and page #:	Vol. 4, Tab U97-2343
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	March 25, 1997
Date of Study completion:	April 8, 1997
Report date:	June 10, 1997
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	Batch A; Purity: N/A

Study Title: Acute Oral (Gavage) Toxicity Study in the Mouse on [redacted] (b) (4) (Project No. 96R036)

Acute toxicity of [redacted] (b) (4) after oral administration was determined in mice. Mice [CD-1(ICRBR), VAF+, 5/sex/dose) were given by oral gavage 250, 500, 1000, 2500, or 5000-mg/kg [redacted] (b) (4) The vehicle was a suspension consisting of 1% CMC and 0.2% Tween 80 suspension. Mortality was observed for up to 14 days. Dose-related increases in mortality were observed. The incidence of deaths (male and female combined) was 0/9, 1/10, 7/10, 10/10 and 10/10 in the 250, 500, 1000, 2500 and 5000-mg/kg groups, respectively. All deaths occurred during the first day after dosing. Signs of toxicity included labored breathing, gasping, ataxia, loss of reflex, tremor, ptosis and vocalization. No signs of toxicity were observed at 250-mg/kg group. The following information is for administrative purpose.

Study No.:	Doc. #U98-3066; Study No. 96R036
Volume #, and page #:	Vol. 5, Tab U98-3066
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	N/A
Date of Study completion:	N/A
Report date:	March 17, 1998
GLP compliance:	Yes, with a signed GLP statement
QA reports:	Yes, with a signed GLP statement
Report Peer Reviewed:	Yes
Drug lot # & purity:	Batch A; Purity: 99.1%

Study Title: Combivent (Albuterol + Ipratropium) plus Degradation Product [redacted] (b) (4) [redacted] 13-Week Inhalation Toxicity Study in Rats

Key Study Finding: Inhalation of [redacted] (b) (4) at a concentration of 2.5% (relative to albuterol) did not increase the toxicity of Combivent inhalation solution in rats. Rats were given by oral inhalation the vehicle (water, G1), albuterol and ipratropium (Combivent, G2), and albuterol and ipratropium spiked with 2.5% of [redacted] (b) (4) (relative to albuterol, G3) for up to 100 minutes. The respective mean pulmonary deposits of albuterol, ipratropium and [redacted] (b) (4) in males and females were 0, 0 and 0 µg/kg/day in Group 1; 154, 31 and 0.17 µg/kg/day in Group 2; 172, 34 and 4.2 µg/kg/day in Group 3. Focal laryngeal squamous metaplasia was observed in the Groups 2 and 3, but not in Group 1. The incidence and severity of the lesions in Groups 2 and 3 were similar.

Study No.:	Doc #U05-1367; Report #664463, Study #23460
Volume #, and page #:	Vol. 5, page N/A; Tab U05-1367
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	October 8, 2003
Date of study completion:	April 22, 2004
Report date:	March 3, 2005
GLP compliance:	Yes, with a signed GLP statement

QA reports: Yes, with a signed GLP statement
Report Peer Reviewed: Yes
Drug lot # & purity: Batches F599503, F599603 & F599703, See Table (below for composition); purity: N/A

Methods: Wistar rats (Han IGS, 10/sex/group) were exposed by nose-only to aerosols of acidified water (Group 1), albuterol and ipratropium (Group 2), or albuterol and ipratropium spiked with [redacted] (b) (4) (2.4% relative to albuterol) up to 90 (females) and 100 minutes (males) daily for 13 weeks. pH of each solution was approximately [redacted] (b) (4) Microscopic examination was done in a complete panel of organs and tissues in all groups. Table 6 presents the composition of testing material in each group. Table 8 presents the concentration of the testing compound in the aerosols during the exposure period.

Table 8 Testing Material Compositions of 13-Wk [redacted] (b) (4) Study in Rats

Group	Batch	Concentration (mg/100 ml)			pH
		Ipratropium	Albuterol	[redacted] (b) (4)	
3	F599603	57.8	288.4	7.5	[redacted] (b) (4)
2	F599503	58.3	290.3	0.3	
1	F599703	0	0	0	

Doses (pulmonary deposits): Albuterol: 0, 154 and 172 µg/kg/day
Ipratropium: 0, 31, and 34 µg/kg/day
[redacted] (b) (4) 0, 0.17, 4.2 µg/kg/day.
Species/strain: Rats, Wistar Han (CRL:WI(GLX/BRL/HAN) IGSBR VAF
Number/sex/group (main study) or time point (main study): 10
Route, formulation, volume and infusion rate: Nose-only inhalation, 80 - 100 and 80 – 90 minutes/day in males and females, respectively
See Table 9 for aerosol drug concentrations
Satellite groups used for recovery: None.
Age: 6 - 7 weeks
Weight (mean): M: 124 - 187g; F: 116-157 g
Unique study design or methodology (if any) Nose-only inhalation, 100 and 90 minutes/day in males and females, respectively.

Table 9 Aerosol Concentrations of Testing Materials in Rats

Group	Aerosol Concentration (µg/L)		
	Ipratropium	Albuterol	[redacted] (b) (4)
1	[redacted]		(b) (4)
2			
3			

a. Derived using the formulation composition data.

Observations and Times:
Clinical signs: Daily
Body weights: Twice weekly

Food consumption:	Weekly
Ophthalmoscopy:	Pre-treatment and week 4
EKG:	Not assessed
Hematology:	Weeks 7 and 13
Clinical chemistry:	Weeks 7 and 13
Urinalysis:	Not done
Gross pathology:	Sacrifice
Organs weights:	Adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thymus, thyroid lobes (with parathyroids) and uterus
Histopathology:	Control and HD groups: a complete panel for all groups; Adequate Battery: yes (x), no ( ) Peer review: yes (x), no ( )
Other:	Chamber aerosol and drug concentrations were measured weekly

Results

Dose estimates: The respective mean pulmonary deposits of albuterol, ipratropium and [redacted] (b) (4) in males and females were 0, 0 and 0 µg/kg/day in Group 1; 154, 31 and 0.17 µg/kg/day in Group 2; 172, 34 and 4.2 µg/kg/day in Group 3. Table 10 summarizes the achieved and pulmonary doses. The achieved dose was estimated using the formula: µg/kg/day = (C x RMV x T) ÷ BW, where C, RMV, T and BW represents aerosol concentration (µg/l), RMV (l/min), the duration of exposure (min) and body weight (kg, weekly mid-week mean). The duration of exposure ranged 80 - 100 minutes/day in both genders. The overall mass mean aerodynamic diameter was [redacted] (b) (4) for Groups 1, 2 and 3 respectively.

Table 10 Exposure Estimates of the 13-Wk [redacted] (b) (4) IH Study in Rats

	Group	Dose (µg/kg/day)								
		Albuterol			Ipratropium			[redacted] (b) (4)		
		M	F	M + F	M	F	M + F	M	F	M + F
Achieved [a]	1	0	0	0	0	0	0	0	0	0
	2	1592 ± 325	1494 ± 314	1543	317 ± 65	298 ± 62	308	1.7 [c]	1.6 [c]	1.7
	3	1775 ± 369	1657 341	1716	353 ± 73	330 ± 67	342	43 ± 9	40 ± 9	42
Pulmonary [b]	1	0	0	0	0	0	0	0	0	0
	2	159	149	154	32	30	31	-	-	0.17
	3	178	166	172	35	33	34	4.3	4.0	4.2

a. Source: Vol. C1.25, page 30.
b. Derived as the 1/10th of achieved dose.
c. Derived using the formulation composition data.

Mortality: No treatment-related effects were observed.

Clinical signs: No treatment-related effects were observed.

Body weights: No treatment-related effects were observed.

Food consumption: No treatment-related effects were observed.

Ophthalmoscopy: No treatment-related effects were observed.

Hematology: No treatment-related effects were observed.

Clinical Chemistry: No treatment-related effects were observed.

Gross pathology: No treatment-related effects were observed.

Organ Weights: No treatment-related effects were observed.

Histopathology: The Combivent treatment, alone or in combination with 2.5% (b) (4) caused squamous metaplasia in the larynx in rats. Table 11 (below) presents the incidence and severity of the lesion. The addition of 2.5% (b) (4) did not significantly affect the toxicity profile of albuterol and ipratropium.

Table 11 Microscopic Findings in Rats

Organ: observation	Severity	Male			Female		
		G1	G2	G3	G1`	G2	G3
Squamous metaplasia, focal	Minimal	0	8	8	0	7	6
	Mild	0	1	0	0	0	2
	Total	0/10	9/10	8/10	0/10	7/10	8/10

Study Title: (b) (4) (b) (4) **Testing for Point-Mutagenic Activity with *Salmonella typhimurium* and *Escherichia coli***

Key Findings: (b) (4) and (b) (4) tested negative in Ames test.

Report/ Study no.:	Doc. #97-2410, Study No. I91009
Volume and page #:	Vol. 6, Tab 97-2410
Conducting laboratory and location:	Department of Nonclinical Drug Safety, Boehringer Ingelheim Pharma GmbH & Co., KG, Biberach, Germany.
Date of study initiation:	February 12, 1997
Date of study completion:	April 11, 1997
Report date:	July 14, 1997
GLP compliance:	Yes, with a signed statement.
QA reports:	yes (x) no ( ), with a signed statement
Drug, lot #, and % purity:	Batch A for both (b) (4) and (b) (4)

Methods

Mutagenicity of (b) (4) and (b) (4) was tested in the Ames test using the direct plate incorporation method. Five strains of bacteria were treated with at concentrations ranging from 10 to 5000 µg/plate in the absence and presence of rat liver S9 fraction at 37°C for 48 hours. The number of revertant colonies was counted manually or by an automated colony counter.

Strains/species/cell line: *S. typhimurium* TA1535, TA1537, TA100, TA98, and *E. coli* WP2uvrA

Doses used in definitive studies: 10, 100, 500, 1500 and 5000 µg/plate for all strains. Each concentration was carried out in triplicate.

Basis for dose selection: The maximum test concentration per guidelines and precipitation.

Controls:
Vehicle: DMSO and culture medium.
Liver microsomes: from rats treated with 500 mg/kg Aroclor for 5 days.
Positive controls: See Table 12 (below)

Incubation and sampling time: Samples were harvested after an incubation period of 48 hours at 37°C.

Table 12 Positive Controls in Ames Test

Strain	- S9 Fraction		+ S9 Fraction	
	Chemical	µg/plate	Chemical	µg/plate
TA 1535	MNNG [a]	2.0	2-aminoanthracene	3.5
TA 1537	9-aminoathracene	80	2-aminoanthracene	3.5
TA 100	2-nitrofluorene	5	2-aminoanthracene	1
TA 98	2-nitrofluorene	5	2-aminoanthracene	0.5
WP2uvrA	ENNG	2.5	2-aminoanthracene	7.5

a. MNNG = 1-Methey-3-nitro-1-nitrosoguanidine; ENNG = 1-ethey-3-nitro-1-nitrosoguanidine.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study is valid. Dose selection of the study was appropriate; the highest concentration of the drug is the maximum recommended concentration (5,000 µg/plate) by current guidelines. Each concentration was carried out in triplicate. Selection and concentrations of positive controls were appropriate. The count method and criteria for positive results were acceptable. Negative and positive controls produced typical results.

Criteria for a positive response is at least a 2-fold (strains with low background counts) or 3-fold (strains with high background counts) increase in the mutant frequency over the mean value of the vehicle control at one or two concentrations.

Study outcome: No remarkable findings were observed in any tester strain. None of the testing concentrations (i.e., up to 5000 µg/plate in each strain) were cytotoxic. No increases in mutant frequency reached or exceeded the above criteria for positive responses. The positive controls yielded typical results. (b) (4) and (b) (4) are considered negative under the testing conditions.

Study Title: (b) (4) **Mutagenicity Testing with *Salmonella typhimurium* TA1535, TA1537, TA98 and TA100 and *Escherichia coli* WP2uvrA (pKM101). Plate incorporation reverse mutation assay with and without metabolic activation (Study No. 96R035)**

Key Findings: (b) (4) tested negative in Ames test.

Report/ Study no.:	Doc. #98-3010, Study No. 96R035
Volume and page #:	Vol. 6, Tab 98-3010
Conducting laboratory and location:	Department of Nonclinical Drug Safety, Beohringer Ingelheim Pharma GmbH & Co., KG, Biberach, Germany.
Date of study initiation:	December 2, 1996
Date of study completion:	December 4, 1996
Report date:	January 19, 1998
GLP compliance:	Yes, with a signed statement.
QA reports:	yes (x) no ( ), with a signed statement
Drug, lot #, and % purity:	Lot 2925-74

Methods

Mutagenicity of (b) (4) was tested in the Ames test using the plate incorporation method. Five strains of bacteria were treated with at concentrations ranging from 3 - 1,000 µg/plate in the absence and presence of rat liver S9 fraction at 37°C for 48 hours. The number of revertant colonies was counted manually or by an automated colony counter.

Strains/species/cell line: *S. typhimurium* TA1535, TA1537, TA100, TA98, and *E. coli* WP2uvrA

Doses used in definitive studies: 3, 10, 30, 100, 300, 1000 µg/plate for all strains. Each concentration was carried out in triplicates.

Basis for dose selection: Precipitates were observed at the maximum test concentration.

Controls:
Vehicle: DMSO and culture medium.
Liver microsomes: from rats treated with 500 mg/kg Aroclor for 5 days.
Positive controls: See Table 13 (below)

Incubation and sampling time: Samples were harvested after an incubation period of 48 hours at 37°C.

Table 13 Positive Controls in Ames Test

Strain	- S9 Fraction		+ S9 Fraction	
	Chemical	µg/plate	Chemical	µg/plate
TA 1535	Sodium azide	10	2-aminoanthracene	1
TA 1537	9-aminoathracene	50	2-aminoanthracene	2
TA 100	Sodium azide	10	2-aminoanthracene	1
TA 98	2-nitrofluorene	1	2-aminoanthracene	1
WP2uvrA	ENNG [a]	0.5	2-aminoanthracene	2

a. ENNG = 1-ethey-3-nitro-1-nitrosoguanidine.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study is valid. Dose selection of the study was appropriate; the top concentration was acceptable because the report states that "(b) (4) was insoluble at dose levels greater or equal to 1000 µg/plate". Each concentration was carried out in triplicate. Selection and concentrations of positive controls were appropriate. The count method and criteria for positive results were acceptable. Negative and positive controls produced typical results.

Criteria for a positive response are: 1) "an increase in the mean mutant numbers to 3x the concurrent vehicle control mean revertant numbers or 20, which ever is greater" for Strains TA1535, TA1537, TA98 and *E. coli"*, and 2) "an increase in the mean mutant numbers to 3x the concurrent vehicle control mean revertant numbers" for Strain TA100.

Study outcome: No significant increases in mutant frequency reached or exceeded the above criteria for positive responses. The positive controls yielded typical results. (b) (4) is considered negative under the testing conditions.

Study Title: (b) (4) (b) (4) Mutagenicity study for chromosomal aberration in human lymphocytes in vitro

Key findings: (b) (4) tested negative in the chromosomal aberration assay in cultured human lymphocytes. (b) (4) concentrations were up to 5,000 µg/ml in the absence or presence of the S9 fraction.

Report/ Study no.:	U04-1247/ 03B2209
Volume and page #:	Vol. 6, Tab U04-1247
Conducting laboratory and location:	Department of Nonclinical Drug Safety, Boehringer Ingelheim Pharma GmbH & Co., KG, Biberach, Germany.
Date of study initiation:	January 9, 2004
GLP compliance:	Yes, with a signed statement.
QA reports:	yes (x) no ( ), with a signed statement
Drug, lot #, and % purity:	0003/RCC 0296B, purity 99.5%

Methods

Human lymphocytes from peripheral blood were exposed to up to 5,000 µg/ml of (b) (4) in the absence or presence of the rat S9 liver enzyme for 4 – 24 hours. The cells were later evaluated for cytotoxicity and chromosomal damages under microscopic examinations. Cytotoxicity was determined by the extent of mitotic index inhibition and cell morphology. Table 14 (next page) presents the chronology of the major events of the study.

Table 14 Chronology of Treatment

S9 fraction	Timing (hr)				
	Culture initiation	(b) (4) Treatment	Colcemid treatment	Harvesting	
				Regular	Delayed
Absent	0	48 - 52	70	72	-
Absent	0	48 - 52	70	72	-
Absent	0	48 - 72	94	-	96
Present	0	48 - 52	70	72	-

-, not evaluated.

a. The (b) (4) concentrations were 100, 1,000 and 5,000 µg/ml for each group except for the delayed harvesting arm which used the 1,000 µg/ml concentration only.

Strains/species/cell line: cultured peripheral human lymphocytes from volunteers.

Doses used in definitive study: 100, 1000 and 5000 µg/ml. (b) (4) concentrations in the dose-ranging study were 3, 30, 30, 10, 1000, 3000, and 5000 µg/ml, respectively; but only the 100, 1,000 and 5,000 concentrations were analyzed.

Basis of dose selection: Solubility and slight toxicity. Precipitates were observed at the 5,000 µg/ml in both dose-ranging and definitive studies. The 5,000 µg/ml concentration group at the regular harvest time also showed a slight (21%) inhibition of mitotic index.

Negative controls: culture medium (chromosomal medium A from (b) (4)

Positive controls: Adriamycin (0.05 µg/ml) and cyclophosphamide (7 µg/ml)

Incubation and sampling times: 4 hours (+/- S9 fraction) and 24 hr (- S9 fraction only). Human lymphocytes (0.25 ml human blood and 2.75 ml culture medium) were incubated for 48 hours in the presence phytohaemagglutinin. The cells were then treated with (b) (4) for 4 – 24 hours by adding the testing material to the medium. Colcemid was added (to a final concentration of 0.2 µg/ml) to arrest the cells in metaphase and the cells were incubated for another 2 hours. The cells were harvested by centrifuging at 1,000 rpm for 10 minutes. The cells were re-suspended in the 0.4% KCl solution and fixed in ice-cold ethanol and glacial acetic acid (3 to 1 ratio). Slides were made from the suspended cells, air-dried and stained with 7% Giemsa.

Results

Study validity (comment on replicates, counting method, criteria for positive results, etc.): The study is a valid assay. Duplication and counting method were acceptable. Duplicate slides were made for each concentration of treatment. Mitotic index was determined from 1,000 cells and the number of polyploidy cells was recorded in 2,000 cells, respectively. Two hundred cells/slide were examined for chromosomal aberrations.

The clastogenicity of the testing material was evaluated by an increase in the percentage of cells showing structural chromosomal aberrations excluding gaps. A positive response was defined as reproducible and concentration-dependent increase in the aberration frequency in the exposed cultures. Acceptance criteria for the assay were that the vehicle control data were within historical ranges and the positive controls show significant increases in the cells with chromosomal aberrations. Statistical analyses were done using Fisher's Exact Test

without adjusting for multiple comparisons. A probability of 5% was considered statistically significant.

Study outcome: [redacted] (b) (4) did not cause any significant increases in chromosomal aberrations in cultured human lymphocytes. [redacted] (b) (4) treatment at concentrations up to 5,000 µg/ml for 4 hours in the absence or presence of the S9 fraction and 24 hours in the absence of the S9 fraction did not result in any increases in the percentage of cells with chromosomal aberrations over the concurrent vehicle control. The value for the vehicle control is well within the historical ranges of the laboratory (0 – 4%). The positive controls caused a typical and statistically significant increase in the percentage of aberrations (23 – 38%).

2.6.6.9 Discussions and Conclusion

Studies reviewed in this document revealed no new, significant nonclinical information about active or inactive ingredients of the Combivent® Respimat® Inhalation Sprays. The application submitted inhalation toxicity studies of albuterol- [redacted] (b) (4) formulation up to 2 weeks in rats and 3 months in dogs. Albuterol [redacted] (b) (4) formulation apparently contains [redacted] (b) (4). The application also submitted a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any new, significant information about any of the three compounds: albuterol, EDTA and benzalkonium chloride.

This document also reviewed general and genetic toxicity studies of two albuterol impurities (i.e., [redacted] (b) (4) and [redacted] (b) (4) [redacted] (b) (4) was evaluated for its genetic toxicity and general toxicity. [redacted] (b) (4) was evaluated for its genotoxicity. The genetic toxicity studies of [redacted] (b) (4) included 2 bacterial mutagenicity assays and a chromosomal aberration assay in human peripheral blood lymphocytes. [redacted] (b) (4) tested negative in each assay. General toxicity of [redacted] (b) (4) was evaluated in a 13-week inhalation toxicity study of albuterol and ipratropium spiked with 2.5% [redacted] (b) (4) (relative to albuterol) in rats. Results showed that the addition of [redacted] (b) (4) did not increase the toxicity of inhaled albuterol and ipratropium. The genotoxicity of [redacted] (b) (4) was evaluated in a bacterial gene mutation assay and the compound tested negative in the test. Relevance and implications of these findings were will discussed in a Chemistry Consultation Review that evaluates the acceptance of impurity specifications.

2.6.6.10 Tables and Figures

Not applicable because no data were submitted.

2.6.7 TOXICOLOGY TABULATED SUMMARY

Not applicable because no data were submitted.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The application has submitted adequate nonclinical safety data to support registration of Combivent® Respimat® Inhalation Sprays. The application proposed to market the product as a replacement of the currently marketed Combivent® Inhalation Solution, a CFC-containing product. Combivent is a combination product of albuterol and ipratropium. The recommended doses of albuterol and ipratropium each from the proposed product were lower than that of the currently marketed product and were of no nonclinical safety concerns. EDTA and benzalkonium as excipients of the formulation have been used in other products (b) (4) The available nonclinical data are considered supportive of the intended use of Combivent® Respimat® Inhalation Sprays. Pending the labeling review, approval of the application is recommended from the nonclinical perspective.

Combivent® Respimat® Inhalation Spray (abbreviated as Combivent® Respimat® for the sake of discussion) is a metered dose oral inhaler. Each actuation of the inhaler releases approximately 20-µg ipratropium bromide and 120-µg albuterol sulfate from the valve. The proposed recommended daily use of the device is 1 actuation four times a day. Patients may take additional doses as needed, but the maximum daily dose should not exceed 6 actuations in 24 hours.

Combivent® CFC Inhalation Aerosol (abbreviated as Combivent® CFC in the discussion), the currently marketed product, is also a metered-dose oral inhaler. Each actuation of the inhaler releases approximately 18-µg ipratropium bromide and 103-µg albuterol sulfate from the value. The recommended daily use of the device is two actuations four times a day. Patients may take additional doses as needed, but the maximum daily dose should not exceed 12 actuations in 24 hours.

Apparently, Combivent® Respimat® delivers the smaller amount of albuterol and ipratropium than Combivent® CFC (Table 15). The respective maximum total daily dose of albuterol sulfate and ipratropium bromide in a patient is 720 and 120 mcg for the Respimat® inhaler and 1236 and 216 mcg for the CFC inhaler. On a unit body weight basis for a 50-kg patient, the respective maximum total daily dose of albuterol sulfate and ipratropium bromide in a patient is 14.4 and 2.4 mcg for the Respimat® inhaler and 24.72 and 4.32 mcg for the CFC inhaler. One-hundred twenty micrograms of albuterol sulfate contains approximately 100-µg albuterol free base.

Table 15 Product and Exposure Characteristics of Combivent® Respimat® and CFC

	Amount released (µg /actuation)		MRHID [a]			
			µg/patient/day [b]		µg/kg/day [c]	
	Albuterol sulfate	Ipratropium bromide	Albuterol sulfate	Ipratropium bromide	Albuterol sulfate	Ipratropium bromide
Respimat	120	20	720	120	14.4	2.4
CFC	103	18	1236	216	24.72	4.32

a. MRHID = the maximum recommended human daily inhalation dose.
b. Calculated from daily doses of 6 and 12 actuations for Respimat and CFC, respectively.
c. Based on a 50-kg patient.

The nonclinical characterization of albuterol and ipratropium has been completed previously. The characterization included the studies of general toxicity, reproductive toxicity, genetic toxicity and carcinogenicity. Findings of these studies have been described in the labeling of the currently marketed Combivent CFC product. The findings will also be described in the labeling of Combivent Respimat. Refer to the labeling for detailed information.

The submission contained no new, significant nonclinical information about either ingredient of the Combivent® Respimat®. Neither did it contain any significant information about its excipients. The application submitted inhalation toxicity studies of albuterol- (b) (4) formulation up to 2 weeks in rats and 3 months in dogs. Albuterol (b) (4) formulation appeared to be a formulation that contains (b) (4) The application also submitted a 13-week inhalation toxicity study of EDTA and benzalkonium chloride in rats. These studies did not reveal any new, significant information about any of the three compounds: albuterol, EDTA and benzalkonium chloride. The Overall Toxicology Summary (Section 2.6.6.1, page 7 - 9) provided a summary of results of these studies. Briefly, the (b) (4) formulation possesses a toxicity profile typical of albuterol and other beta adrenergic agonists. The target organs of toxicity were the heart, liver and testis. The inhalation of EDTA and benzalkonium chloride, alone or in combination, caused squamous metaplasia in the larynx and goblet cell hyperplasia in the nasal cavity. The findings associated with the excipients were either rat specific and/or irrelevant to the current application. Overall, the findings of the newly submitted studies did not reveal any new findings that are of safety concerns from the nonclinical perspective.

This review also evaluates general and genetic toxicities of some drug impurities and degradants. Implication and relevance of the findings of the studies are discussed in a Chemistry Consultation Review evaluating the proposed specifications of impurities in drug substance and products.

The proposed daily dose of albuterol and ipratropium from the Combivent Respimat Inhalation Spray is a portion of that from the Combivent Inhalation Aerosol, the currently marketed CFC product. The newly submitted toxicity studies of albuterol and excipients did not reveal any new and significant findings that are of nonclinical safety concern about the to-be-marketed product. The approval of the drug is recommended pending the labeling review.

Unresolved toxicology issues (if any): None.

Recommendations:

Approval of Combivent® Respimat® Inhalation Sprays is recommended from the nonclinical discipline, pending the labeling review which will be completed later in consultation with the clinical discipline.

Labeling Review

The review of the nonclinical sections of the draft labeling will be completed at a later time when the clinical information is finalized. The application submitted a proposed draft of the labeling. The draft appeared compliant with the current labeling initiative. The nonclinical edits to the draft labeling appeared minimal, although dose ratios between animals and human may need revision. The clinical discipline does not appear ready to complete the labeling review at this time. A nonclinical review of the labeling does not appear necessary at the present time given the uncertainty of the clinical discipline. A review will be completed later in consultation with the clinical discipline.

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

Luqi Pei
4/14/2009 02:54:21 PM
PHARMACOLOGIST

Molly Shea
4/14/2009 02:56:25 PM
PHARMACOLOGIST
I concur.

DIVISION OF PULMONARY AND ALLERGY PRODUCTS PHARMACOLOGY AND TOXICOLOGY CONSULTATION

Date:	March 31, 2009
To:	Alan Schroeder, Ph.D., Chemist Office of New Drug Quality Assurance /DPA I, CDER
From:	Luqi Pei, Ph.D., Senior Pharmacologist Division of Pulmonary and Allergy Products, CDER
Through:	Molly Shea, Ph.D., Acting Supervisory Pharmacologist Division of Pulmonary and Allergy Products, CDER
Subject:	Safety Evaluations of Drug Impurities and Degradants in Combivent® Respimat® Inhalation Sprays

General Information

NDA/IND#:	NDA 21-747 Chemistry Consultation Review No. 1
Sponsor:	Boehringer Ingelheim, Inc.
Drug Product:	Combivent Respimat Inhalation Spray

Summary: There were no nonclinical safety concerns about the proposed specifications of any drug impurities, extractable, leachables, particulate matters and volatile residues. A number of compounds were reported as degradants or impurities of albuterol and ipratropium in drug substances and drug product. Also reported were leachables, particulate matters and volatile residues in the drug product. The proposed specifications of each impurity in drug substance had been considered acceptable previously. Several impurities in the drug product were discussed because of their high concentrations or genetic toxicity. The available data do not suggest any safety concerns about the level of drug impurities, leachables, extractables, particulate matters and volatile residues.

Materials Reviewed

(b) (4) (Degradation product of Salbutamol) Acute Intravenous Toxicity Study in Mice
Acute Oral (Gavage) Toxicity Study in the Mouse on (b) (4) (Project No. 96R036)
(b) (4) Testing for Point-Mutagenic Activity with Salmonella typhimurium and Escherichia coli
(b) (4) Mutagenicity Testing with S. typhimurium TA1535, TA1537, TA98 and TA100 and Escherichia coli WP2 uvrA tpKM101) Plate Incorporation Reverse Mutation Assay with and without Metabolic Activation)

(b) (4) Mutagenicity Testing with S. typhimurium TA1535, TA1537, TA98 and TA100 and Escherichia coli WP2 uvrA tpKM101) Plate Incorporation Reverse Mutation Assay with and without Metabolic Activation)

(b) (4) Mutagenicity Study fòr Chromosomal Aberrations in Human Lymphocytes In Vitro

Introduction

This review was generated in response to the Chemistry Consultation Requests issued by Dr. Alan Schroeder of ONDQA on December 31, 2008 and February 5, 2009 and by Dr. Ali Al-Harkim on March 20, 2009, respectively. The 31-DEC-2008 request was for the safety evaluation of impurity specifications and particulate matters in the drug product. The 05-FEB-2009 request (via email) was for the safety evaluation of impurities in drug substance. The 20-MAR-2009 request provided updates to the two previous requests. It also requested safety evaluations of leachables and extractables of the device. The 20-MAR-2009 request stated that the drug substance specifications of the current application were identical to what the Agency had found acceptable previously in NDA 20-291 (Combivent® Inhalation Aerosol). On March 27, 2009, Dr. Schroeder provided via an email message an update of the 20-MAR-2009 request regarding the estimated daily intakes of leachables and extractables of the device. Dr. Schroeder also updated impurities specifications via an email message on March 30, 2009.

(b) (4)

Figure 1 Decomposition Pathways of Albuterol

Table 1 Impurities and Degradants in Combivent Respimat Inhalation Spray

Impurity		Concentration		
Code	Name	Drug Substance [a]	Drug Product [b]	Exposure [d] (µg/pts/day)
				(b) (4)

a. Values provided by Dr. Alan Schroeder on 30-MAR-2009 (via email) as an update to the 05-FEB-2009.
b. Extracted from Chemistry Consultation Request by Dr. Alan Schroeder dated December 31, 2008.
c. Extracted from Chemistry Consultation Request by Dr. Alan Schroeder dated December 31, 2008.
d. (b) (4)
e. Daily exposures of impurity levels were based on daily doses of 600-mg albuterol and 120 mg ipratropium bromide, respectively, exvalve. The maximum recommended daily human inhalation dose of Combivent Respimat was not exceeding 6 actuations within 24 hours. Each actuation releases 100-mg albuterol and 20-µg ipratropium bromide from the mouth piece of the device.

A number of albuterol and ipratropium impurities were reported in the drug substance and drug product of Combivent® Respimat® Inhalation Spray (NDA 21-747). Table 1 (above) presents proposed impurity specifications in drug substance and product. Figures 1 (previous page) and 2 (page 4) present the decomposition pathways of albuterol and ipratropium, and structures of major impurities.

Data in Table 1 (above) indicate that three albuterol impurities had specifications exceeding the qualification thresholds of (b) (4) in the drug substance and product, respectively. The impurities were (b) (4) Their proposed specifications ranged between (b) (4) in drug substance and only (b) (4) was present in the drug product. Two additional impurities with specifications below or equal to the ICH qualification thresholds will be discussed in

the review due to being genotoxic or containing structural alerts for genetic toxicity. These two impurities are (b) (4)

(b) (4)

Figure 2 Decomposition pathways of ipratropium

The review evaluates only the above five compounds. Reasons for omitting the remaining impurities are three fold: 1) None of the proposed specifications were above the ICH qualification thresholds. 2) None of the compounds carried structural alerts for genotoxicity. 3) Their exposure levels were low; with exception of (b) (4)), their daily exposures of (b) (4) µg/patient/day were only a fraction of the allowable limit of 1.5 µg/day for even genotoxic impurities. (b) (4) is not genotoxic (Ref.: Report #U97-2410) or has no structural alert for genotoxicity.

Evaluation

This review conducts safety evaluations of drug impurities, extractables and leachables using one or more of the following approaches.

1. The proposed specification of a compound will be considered acceptable if the daily intake of the compound is not more than (i.e., ≤) 1.5 µg/patient, regardless the genotoxic potential. This approach was based on the recent draft guidance for industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approach (2008).
2. The compound is non-mutagenic or lacks any structural alerts for genotoxic potential and its proposed specification is ≤ 1.0% in the drug product, respectively. This approach was based on the ICH Q3B(R) guidance for industry: Impurities in New Drug Products (2006).

3. The compound is non-mutagenic, its proposed specification in the drug product is greater than 1.0%, and the sponsor had conducted appropriate species to support the specification.

Drug substance impurities:

The review did not evaluate drug substance impurities because the same specifications had been found acceptable previously, according to the 20-MAR-2009 request. A number of drug impurities were reported in the drug substance. As listed in Table 1, albuterol impurities included (b) (4) The ipratropium impurities included (b) (4) Among them, only four albuterol impurities (b) (4) had specifications exceeding the ICH qualification threshold for drug substance (≤ 0.15%). Their specifications (b) (4) however, were identical to what the Agency had found acceptable previously in the drug substance in NDA 20-291 (Combivent Inhalation Aerosol). There was no new, additional information suggesting any need for modifying the previous specifications. No additional discussion of the drug substance is needed.

Drug Product Impurities:

The drug product also contained the albuterol and ipratropium impurities, but the number of impurities in the drug product was smaller than drug substance. The concentrations of some impurities were, however, slightly higher; only the level of one impurity exceeded the qualification threshold of 1.0%. This impurity, namely (b) (4), had a proposed specification of (b) (4). The current review evaluates the safety of the (b) (4) level. It also evaluates (b) (4) due to their genotoxicity potentials. The review will not discuss the remaining drug product impurities because: 1) their proposed specifications (b) (4) were compliant with the ICH qualification threshold of ≤ 1.0%, and 2) there were no structural alerts for genotoxic potential.

(b) (4)

There is no nonclinical safety concern about the proposed specifications of (b) (4) in the drug product. The proposed (b) (4) level was greater than the ICH qualification threshold of 1.0% in drug product, but the applicant had conducted appropriate qualification toxicity studies to support the specification.

The applicant submitted genetic toxicity and general toxicity studies of (b) (4) to qualify the compound. Genetic toxicity studies included 2 bacterial mutagenicity assays and a chromosomal aberration assay in human peripheral blood lymphocytes. General toxicity studies included in a 13-week inhalation toxicity study of albuterol and

ipratropium spiked with (b) (4) (relative to albuterol). Comprehensive reviews of these studies can be found in the original NDA 21-747 pharmacology and toxicology review which will be completed soon. The following discussions briefly summarize the findings and evaluate the adequacy of the studies in support of the proposed specifications.

(b) (4) was not genotoxic. Report 97-2410 showed that both (b) (4) tested negative at concentrations up to 5,000 µg/plate in a bacterial gene mutation testing. Report U98-3010 showed that (b) (4) tested negative at concentrations up to 1,000 µg/plate in the same bacterial gene mutation testing. Report U04-1247 showed that (b) (4) tested negative at concentrations up to 5,000 µg/ml in the chromosomal aberration assay in cultured human lymphocytes.

Acute toxicity of (b) (4) was evaluated after oral and intravenous administration in mice. Report U97-2343 showed that the median lethal dose (LD_{50}) of (b) (4) after intravenous administration was 7.4 mg/kg, although no deaths occurred at 5 mg/kg (n = 5 /sex) in mice. Report U98-3066 showed that (b) (4) after oral administration in mice was lethal at ≥ 500 mg/kg, but not at 250 mg/kg.

General toxicity of (b) (4) was evaluated in a 13-week inhalation toxicity study in rats (Report U05-1367). Rats were given by inhalation the vehicle (water, G1), albuterol and ipratropium (Combivent, G2), or Combivent spiked with (b) (4) of (b) (4) (relative to albuterol, (b) (4)) for up to 100 minutes/day. The respective mean pulmonary deposits of albuterol, ipratropium and (b) (4) in males and females were 0, 0 and 0 µg/kg/day in Group 1; 154, 31 and 0.17 µg/kg/day in Group 2; 172, 34 and 4.2 µg/kg/day in Group 3. The amount of (b) (4) in Group 2 was apparently attributed to the trace amount associated with the aqueous formulation. Focal laryngeal squamous metaplasia was observed in the Groups 2 and 3, but not in Group 1. The incidence and severity of the lesions in Groups 2 and 3 were similar. The results indicated that inhalation of (b) (4) at a concentration of (b) (4) (relative to albuterol) did not increase the toxicity of Combivent inhalation solution in rats.

Overall, (b) (4) was non-genotoxic. The compound at the (b) (4) level (relative to albuterol) did not increase the toxicity of inhaled albuterol and ipratropium in a 13-week inhalation study. The available nonclinical data were considered adequate to qualify the proposed specification of (b) (4) in the drug product.

(b) (4)

There is no nonclinical safety concern about (b) (4) specification (b) (4) in the drug product. (b) (4) (also coded as (b) (4) in some reports) is genotoxic as previously reported by this sponsor and other sponsors. The proposed specification of (b) (4) in the drug product was identical to what the Division has allowed for other albuterol products. The daily exposure of (b) (4) from the current product in a patient (b) (4) µg/day), however, was not only below the qualification of 1.5 µg but also a fraction of that from inhalation (nebulized) solutions. Thus, there is no safety concern about (b) (4) (b) (4) in the Combivent Respimat.

(b) (4)

There is no nonclinical safety concern about the proposed specification of (b) (4) (b) (4) carries a structural alert for genetic toxicity potential.[1] The proposed specification of (b) (4) in the drug product was (b) (4) This level corresponded to a total daily exposure of (b) (4) µg/patient. The level is acceptable because it was below the qualification threshold of 1.5 µg/day.

Leachables and extractables:

The 20-MAR-209 request identified a total of (b) (4) compounds as leachables in the product. They are (b) (4)

Table 2 Leachables and Their Estimated Daily Intakes

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

a. Values provided by Dr. Alan Schroeder on March 27, 2009 (via email) as an update to the 20-MAR-2009 request.

(b) (4) Dr. Luqi Pei completed the safety evaluations of the leachables and extractables (b) (4) and found the leachable and extractable profiles acceptable. Another review of the leachable and extractable profile of the device would not be necessary under normal circumstance. The current review conducted additional evaluations of the leachables and extractables for the following two reasons: a) different amounts of leachables and extractables were revealed (b) (4) and b) the recommended maximum daily use of the device changed (b) (4)

[1] The Chemistry Consultation Requests dated 31-DEC-2008 and 20-MAR-2009 were inconsistent regarding the structural alert for genotoxic potential. The 31-DEC-2008 request stated that (b) (4) may carry structural alert for genotoxicity. The 20-MAR-2009 request stated that the compound did not carry a structural alert for genotoxicity. Dr. Alan Schroeder confirmed on 23-MAR-2009 (via email) that (b) (4) did carry a structural alert.

(b) (4). Table 2 presents the estimated leachables and their maximum daily exposure levels.

None of the leachables and extractables was above the allowable daily intake of 1.5 µg/day. (The highest daily exposure of the extractable was approximately (b) (4) Neither included structural alerts for genetic toxicity. There is no nonclinical concern about the proposed specifications of the leachables and extractables.

Particulate matters:

The 31-DEC-2008 request sought for the safety evaluations of particulate matters. The request states that the proposed specifications for the particulate matters was per individual canister (b) (4) for the particulate matters with mean diameters of (b) (4) respectively. According to Chemistry Consult Review completed on May 6, 2008 in NDA 21-395, the mean weight per particle was (b) (4) ng for each small, mid and large particle, respectively. The respectively proposed specifications of small, mid and large particles corresponded to (b) (4) µg per canister in total weights and (b) (4) µg/day in exposure per subject. The mid and large size particles were of no particular safety concern because they are not only in small quantity (b) (4) µg/patient/day) but also not-expected to reach the pulmonary region. The estimated exposure of a patient to small size particles were of no safety concern either because of the negligible quantity (b) (4) µg/day).

Excipients:

There is no nonclinical safety concern about any of the excipients used in the product. The safety evaluations of excipients are covered in the original pharmacology and toxicology review. The current review addresses EDTA, an excipient in Combivent Respimat per the 20-MAR-2009 request. (b) (4) The original pharmacology and toxicology review of the application to-be-completed soon will be concluded. Briefly, there is no nonclinical safety concern about the EDTA concentration in Combivent® Respimat® because the same proposed concentration has been approved in other products and the total amount of EDTA exposure is expected to be a small fraction of some marketed products.

Conclusion

The nonclinical evaluations as discussed above found no safety concerns about any of the proposed specifications of drug impurities and degradants, leachables, extractables, metals, volatile residues and particulate matters in Combivent® Respimat® Inhalation Spray.

Luqi Pei, Ph.D,
Senior Pharmacologist

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/s/

Luqi Pei
3/31/2009 08:33:29 AM
PHARMACOLOGIST

Molly Shea
3/31/2009 08:36:36 AM
PHARMACOLOGIST
I concur.

2.6 PHARMACOLOGY / TOXICOLOGY REVIEW

NDA 21-Day Pharmacology Fileability Check List

Reviewer: Luqi Pei, Ph.D.

NDA No: 21-747
Drug Name: Combivent Respimat
Date of submission: October 9, 2008 (stamp date)
Date of 45-day file-ability meeting: November 13, 2008
Information to the Sponsor: None.
Date of check list: November 4, 2008

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

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

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

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

* The application contains reports of a 13-week inhalation toxicity study of Combivent spiked with degradants, short-term inhalation toxicity studies and genetic toxicity studies of impurities and degradants, (b) (4) (albuterol) formulation studies up to 2-week and 13-week in rats and dogs, and a 13-week inhalation toxicity study of benzalkonium chloride and EDTA in rats. The submission also contains a 2-yr carcinogenicity study of tiotropium in rats which has been reviewed in NDA 21-395.

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

If no, state why not: The to-be-marketed formulation and the formulation used in 13-

13-week inhalation toxicity study of Combivent spiked with degradants are identical.

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

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

Yes. The label does follow the new product labeling recommendations (PLR). Dose ratios between animals and humans in preclinical sections (carcinogenesis, mutagenesis and impairment of fertility, pregnancy category and overdosage) are appropriate as they are expressed in either mg/m^2. Edits to the proposed labeling is necessary, the review will address the edits.

(6) Has the applicant submitted all special studies/data requested by the Division prior to the submission including but not limited to pre-NDA discussion? Yes. The Division has determined in the 10-MAY-2002 and 26-MAY-2006 End-of-Phase 2 meetings (IND 57948) that no additional toxicity studies of the active ingredients are needed.

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

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

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

(9) Has the applicant submitted any studies or data to address any impurity or extractable issues (if any)? Yes. The application submitted reports of a 13-week inhalation toxicity study of Combivent spiked with degradants, short-term inhalation toxicity studies and genetic toxicity studies of impurities and degradants.

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

If yes, identify those below

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

If no, state below why it is not.

If yes, should any additional information/data be requested? No.

If yes, identify those below.

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

/s/

Luqi Pei
12/8/2008 07:43:16 PM
PHARMACOLOGIST

Timothy Robison
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