CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-395

CHEMISTRY REVIEW(S)

NDA 21-395
Review #2

Spiriva® Handihaler®
(tiotropium bromide inhalation powder)

Boehringer Ingelheim Pharmaceuticals, Inc.

Alan C. Schroeder, Ph.D.
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-395

2. REVIEW #: 2

3. REVIEW DATE: 16-Jan-2004

4. REVIEWER: Alan C. Schroeder, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	12-DEC-2001
Amendment	12-APR-2002
Amendment (Stability Update)	06-AUG-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (AC/resubmission)	31-JUL-2003
Amendment (BC/ [redacted] stability, modified package)	22-AUG-2003
Amendment (BC/ [redacted] stability, modified package)	05-NOV-2003
Amendment (BC)-response to first IR letter (CMC)	04-DEC-2003
Amendment (BZ)-response to 2nd IR letter (CMC)	16-DEC-2003
Amendment (BL)- CMC responses to individual requests & labeling	30-DEC-2003
Amendment (BC) – response to 3rd IR letter (CMC)	05-JAN-2004
Amendment (BL)	08-JAN-2004
Amendment (BL)	14-JAN-2004 (sent by e-mail)
Amendment (BZ) – commitments	15-JAN-2004 (sent by e-mail)
Amendment (BC) – change in accept. criteria for degradant	15-JAN-2004 (sent by e-mail)

7. NAME & ADDRESS OF APPLICANT:

Name: Boehringer Ingelheim Pharmaceuticals, Inc.

Address: 900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Representative: Peter Fernandes, M. Pharm
Director, Drug Regulatory Affairs
203-798-5337
Telephone: 203-512-3146 (cell)
203-791-6262 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Spiriva® HandiHaler®
b) Non-Proprietary Name (USAN): tiotropium bromide inhalation powder
c) Code Name/# (ONDC only): Ba 679 BR
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: anticholinergic with specificity for muscarinic receptors.

11. DOSAGE FORM: Inhalation Powder (Pre-Metered DPI)

12. STRENGTH/POTENCY: 10.4 µg (as the anhydrous cation) per inhalation from the mouthpiece. 18 µg (as the anhydrous cation) or 22.5 µg (as tiotropium bromide monohydrate) metered in each capsule.

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_ Rx ___ OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

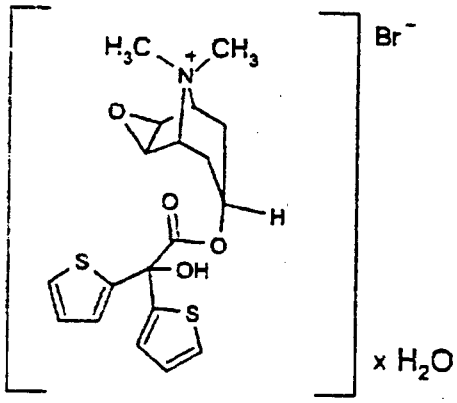
_____SPOTS product – Form Completed

___X___Not a SPOTS product

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Drug Substance chemical name is

(1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, monohydrate

CAS 139404-48-1



Molecular formula: $C_{19}H_{24}BrNO_5S_2Br \times H_20$

Molecular Mass: (M_r): 490.4 (hydrate) 472.41 (anhydrous)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs: (reviewed/assessed by Dr. Arthur Shaw in this review cycle)

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]
	IV			7	No review necessary.
	III			1	DMF inadequate (16 Dec 2003) but adequate data for is in NDA. See Response 15a, pg. 59 of this review for justification. Also product not consumed.
	IV			3	Adequate (01-Jul-1999)
	III			3	Adequate (12-Feb-2003)
	III			1	Adequate Review 03-Oct-2003
	III			1	Adequate Review 15-Jan-2004
	III			1	Adequate (03 Dec 2003) – updates not reviewed because review was not necessary for this NDA – this is used for
	III			1	Adequate Review 05-Jan-2004
	III			3	Adequate (9-Aug-1999)
	III			3	Adequate (15-Oct-2002) Note: 17-Nov-2003 update is inconsequential
	III			1	Review not yet finalized, but the only deficiency is addressed in the NDA.
	IV			1	Adequate review dated 14-Jan-2004

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N/A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	46,687	BI	Tiotropium Bromide Inhalation Powder
IND	[redacted]		[redacted]

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is NOT APPROVABLE from a CMC standpoint.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

No recommendations at this time

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Drug Substance:

Tiotropium is a white to yellowish-white powder. Melting occurs at about — using
The structure of tiotropium has been determined by

.ll data are consistent with the assigned structure. Tiotropium is a quaternary ammonium compound. There are no other ionizable or dissociable groups in the molecule besides the positively charged quaternary nitrogen. The aqueous solubility of the compound is about . at room temperature, independent of pH. The pH of a saturated solution in water is and the pH of a 1% aqueous solution is between The drug substance is more soluble in such as methanol and , but practically insoluble in

Drug Substance-Related Issues:

1. The applicant needs to submit a DMF reference for the

2. The applicant considers the tiotropium bromide as the drug substance. They consider the drug substance as a drug product . In this review, all forms of tiotropium bromide are considered the drug substance and the associated discussions are appropriately located.

3. There is a noticeable difference in Particle Size between the batches of drug substance manufactured in 1997 (270343 and 270344), and those manufactured in 1999 (290247, 209248, 290249, and 290250). The applicant has been asked to provide an explanation to this discrepancy between the two manufacturing processes used during these time frames.

4. The data show that the drug substance is

5. The applicant needs to provide a detailed procedure for of the tiotropium bromide.

6. No Master Batch Record for manufacture of the drug substance has been submitted.

Drug Product:

Tiotropium Inhalation Powder, Hard Capsules 18 µg, proposed for marketing under the trade name SPIRIVA, consist of a two-piece, imprinted light green opaque hard gelatin capsule containing a powder mixture. This powder mixture is composed of Tiotropium Bromide Monohydrate combined with an inert carrier (lactose monohydrate). Each capsule contains a pre-metered dose of 18 µg tiotropium as the anhydrous cation. The drug delivery is 10.4 µg (as the anhydrous cation) per inhalation from the mouthpiece. The capsules will be packaged into moisture resistant foil blisters.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	Evaluation of stability data for proposed 18-month expiry for drug product	Consult requested informally	18 month expiry acceptable F. Zhou	Completed 12/23/03
EES	Establishment Inspection	3/11/02	Acceptable S. Ferguson 8/29/03	
Pharm Tox	Impurities levels consult	6/24/02	Completed LPei	Completed 8/28/02. Reviewer found the provided data are insufficient to support the safety of the degradant levels in the drug product. Second review completed 12/8/03. Additional safety data are needed if the any of the acceptance criteria for degradants [redacted] are set to allow a maximum above [redacted] (Currently the acceptance criteria would allow [redacted] degradants to be present above the level of [redacted] This was discussed with the applicant in a telecon on January 13, 2004.
			(satisfactory from CMC perspective)	Applicant responded with a 1/15/04 commitment to perform a qualification study for degradants [redacted], and to develop a specific method and acceptance criterion for [redacted] See pg. 53 of this review. In an e-mail message dated 16-Jan-2004, Dr. Luqi Pei stated that the pharmacologists agree with the [redacted]
	Foreign particulates (d.p.) consult	10/21/2003 (e-mail request)	Completed/LPei Acceptable.	Completed 11/18/03. E-mail (see end of review) message dated 11/21/03 expands the conclusion of safety for the foreign particulate acceptance to particles [redacted] and larger, as well as particles below [redacted]
Biopharm	N/A	N/A	N/A	No biopharm issues
LNC	Evaluation of "Spiriva"	2/22/02	Acceptable N. Roselle DMETS: Pending for "Spiriva HandiHaler"	Updated consult request sent to DMETS on 1/15/04 by PM, to evaluate "Spiriva HandiHaler" name.
Methods Validation	MV Package	-	Needs to be updated	Will be forwarded to FDA lab when updated
OPDRA				
EA	N/A	N/A	N/A	Applicant requested a Categorical Exclusion; found acceptable in CR#1.
Microbiology	N/A	N/A	N/A	No consult needed

The Chemistry Review for NDA 21-395

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application may be approved from a CMC standpoint.

Note that a response is pending from DMETS for Mr. Zeccola's consult dated 1/15/04, pertaining to the name "Spiriva HandiHaler." DMETS previously found the name "Spiriva" to be acceptable.

Official submissions should be compared with E-mailed submissions of the last few days, prior to approval of this application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

For a list of CMC agreements, see Response 12 to the January 5, 2004 amendment (pg. 145).

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Drug Substance:

Tiotropium is a white to yellowish-white powder. Melting occurs at about — using —
The structure of tiotropium has been determined by — , i.e.,
— All data are consistent with the assigned structure. Tiotropium is a quaternary ammonium salt. There are no other ionizable or dissociable groups in the molecule besides the positively charged quaternary nitrogen. The aqueous solubility of the compound is about — at room temperature, independent of pH. The pH of a saturated solution in water is — and the pH of a 1% aqueous solution is between — The drug substance is more soluble in — such as methanol —, but practically insoluble in —

Drug Substance-Related Information:

1. The applicant considers the — tiotropium bromide as the drug substance. They consider the — drug substance as a drug product —
2. The data show that the — drug substance is —

Drug Product:

Tiotropium Bromide Inhalation Powder, Hard Capsule 18 µg, proposed for marketing under the trade name Spiriva HandiHaler, consists of a two-piece, imprinted light green opaque hard gelatin capsule containing a powder mixture. This powder mixture is composed of — Tiotropium Bromide Monohydrate combined with an inert carrier (lactose monohydrate). — lactose monohydrate are present in the formulation. The lactose monohydrate in the formulation consists of — lactose. The — actose is —

Each capsule contains a pre-metered dose of 18 µg tiotropium as the anhydrous cation (equal to 22.5 µg as the tiotropium bromide monohydrate). Each capsule contains a total formulation weight of . The drug delivery is 10.4 µg (as the anhydrous cation) per inhalation from the mouthpiece. The capsules will be packaged into moisture resistant foil blisters. The blisters consist of an aluminum based peeling foil, a polyvinylchloride forming film that is molded into separate cavities each holding a single capsule and an aluminum based protective bottom foil. The second element of the drug product is the HandiHaler device that enables extraction of the dose from the capsules and dispersion of the drug substance in the inhalation air stream of a patient. The HandiHaler holds one capsule at a time, which the patient punctures by pressing a button on the outside of the device, before inhaling. The Tiotropium Hard Capsules are single use only whereas the HandiHaler device is to be used multiple times, however a new HandiHaler will be marketed with each presentation of drug product (i.e., packages of 6 and 30 capsules in blisters).

Drug Product-Related Information (updated per 1/5/2004 amendment):

C

2. After filling,

3. Packaging in the blisters is done

4. The design of the aluminum laminate blisters has been changed since the original NDA capsules/blister) at the Agency's request. The reason for this is to provide more assurance that the patient will not accidentally remove the aluminum lidding foil from more than one capsule at a time, which may result in an inadequate dose ; of stability data are available to date on the new packaging configuration blister). Applicant has

5. The drug product capsules are relatively unstable in a humid environment, once they are removed from the protective blister packaging.

6. Because of capsule instability when unprotected, labeling was modified to state that the drug should be used immediately after the packaging over an individual capsule is opened, or else its effectiveness may be reduced.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used as an inhalation powder drug product consisting of a delivery device (HandiHaler) and separate pre-metered capsule dosage units. It is expected that patients will use the device to provide 10.4 µg of tiotropium once a day for long-term maintenance of COPD.

C. Basis for Not-Approval Recommendation

III. Administrative

A. Reviewer's Signature

See electronic signature page attached to this review in DFS.

B. Endorsement Block

ASchroeder/Date: 16-January-2004
CBertha/Date
AZeccola/Date

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

163 Page(s) Withheld

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

/s/

Alan Schroeder
1/16/04 03:00:31 PM
CHEMIST

Craig Bertha
1/16/04 03:05:28 PM
CHEMIST
I concur.

NDA 21-395

SPIRIVA (tiotropium bromide) Inhalation Powder

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Boeringer Ingelheim Pharmaceuticals, Inc.

Indication: COPD

Presentations: Blisters [redacted]

EER Status: acceptable 3-DEC-2002

Consults: OCPB - no review provided
DMETS – SPIRIVA is acceptable
Statistics –

SPIRIVA was submitted 12-DEC-2001.

SPIRIVA is provided as capsules of 22.5 mcg equivalent to 18 mcg anhydrous which is administered in the HandiHaler device by piercing the capsule allowing the product be inhaled. The actual amount of product administered/capsule is 10.4 mcg at a flow rate of 39 L/min for 6.2 seconds.

The **drug substance** is manufactured by Boeringer Ingelheim in Germany and the Netherlands. The drug substance has been adequately characterized. [redacted] has been identified as the [redacted] which is not considered acceptable The DS is produced [redacted] Inadequate information was provided to evaluate in-process controls. [redacted] impurities were identified and specified, and a sum of all established at [redacted]. The specification is found acceptable with the exception of particle size distribution, [redacted] impurity acceptance criteria. A re-test period of [redacted] is supported by submitted stability data.

Conclusion
Drug substance is not acceptable – several deficiency comments will be sent.

The **drug product** is formulated with [redacted] lactose monohydrate in green opaque capsules. The capsule manufacturing process is a [redacted] process. A DMF is needed for [redacted]. The product is manufactured at the Boeringer Ingelheim Ingelheim am Rhein facility. The manufacturing process and controls are considered acceptable. Packaging DMFs were found deficient. Specifications are considered in-adequate with

several deficiency comments to be sent. – most notable are the impurity acceptance criteria due to in-adequate tox/safety qualification studies. The HandiHaler device is manufactured by [redacted]. Inspection of this facility was cancelled by OC, but this will need to be reactivated. Several component related DMFs were found deficient, as were the extractables data provided. Additional data will be required on daily dose delivered as a function of use – there is apparent charge build-up.

Expiry of [redacted], is proposed however additional stability data are requested.

Conclusion
Drug product and device is not acceptable – several deficiency comments will be sent.

Overall Conclusion
From a CMC perspective the application is reccomended for a not approvable action.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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

/s/

Eric Duffy
12/20/02 02:27:18 PM
CHEMIST

CHEMISTRY REVIEW

NDA 21-395
Review #1

Spiriva (tiotropium bromide) Inhalation Powder

Boehringer Ingelheim Pharmaceuticals, Inc.

Brian Rogers
Division of Pulmonary and Allergy Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-395

2. REVIEW #: 1

3. REVIEW DATE: 20-NOV-2002

4. REVIEWER: Brian Rogers

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
None	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12-DEC-2001
Amendment	12-APR-2002
Amendment (Stability Update)	06-AUG-2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Address:	900 Ridgebury Road P.O. Box 368 Ridgefield, CT 06877
Representative:	Peter Fernandes, M. Pharm Director, Drug Regulatory Affairs 203-798-5337
Telephone:	203-512-3146 (cell) 203-791-6262 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:	Spiriva
b) Non-Proprietary Name (USAN):	tiotropium bromide inhalation powder

c) Code Name/# (ONDC only): Ba 679 BR
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOLOGICAL CATEGORY: anticholinergic with specificity for muscarinic receptors.

11. DOSAGE FORM: Inhalation Powder (Pre-Metered DPI)

12. STRENGTH/POTENCY: 10.4 µg (as the anhydrous cation) per inhalation from the mouthpiece. 18 µg (as the anhydrous cation) metered in each capsule.

13. ROUTE OF ADMINISTRATION: Oral Inhalation

14. Rx/OTC DISPENSED: _X_Rx ___OTC

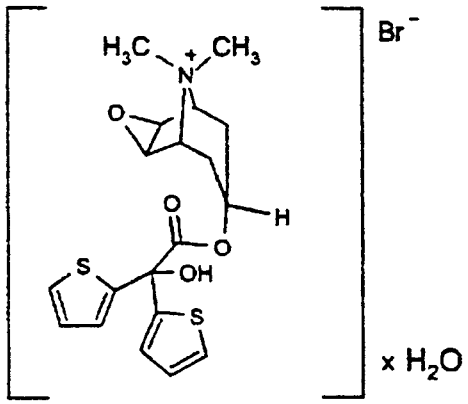
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: Drug Substance chemical name is (1α, 2β, 4β, 5α, 7β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide, monohydrate

CAS 139404-48-1



Molecular formula: $C_{19}H_{24}BrNO_5S_2Br \times H_20$

Molecular Mass: (M_r): 490.4 (hydrate) 472.41 (anhydrous)

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE [note30][1]	STATUS [note31][2]	DATE REVIEW COMPLETED	COMMENTS[3]
	IV			1	Inadequate	10/3/02 (C. Bertha)	LOA 7/11/01
	III			1	Inadequate	10/24/02 (C. Bertha)	LOA 10/10/01
	IV			3	Adequate	7/29/99 (D. Klein)	LOA 8/22/01
	III			3	Adequate	10/2/97 (K. Srinivasachar)	LOA 9/17/89
	III			1	Inadequate	10/8/02 (C. Bertha)	LOA 10/23/01
	III			1	Inadequate	10/24/02 (C. Bertha)	LOA 9/17/01
	III			1	Adequate	10/8/02 (C. Bertha)	LOA 10/23/01
	III			1	Inadequate	10/4/02 (C. Bertha)	LOA 10/12/92
	III			3	Adequate	8/9/99 (M. Ysem, HFD-180)	LOA 4/5/01
	III			1	Adequate	10/11/02 (C. Bertha)	LOA 10/30/01
	III			1	Inadequate	10/29/02 (C. Bertha)	LOA 11/12/01

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 -Type I DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There are enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
N A					

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	46.687	BI	Tiotropium Bromide Inhalation Powder
IND	[redacted]		

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics				
EES	Establishment Inspection	3/11/02	Incomplete	Inspections have been scheduled for sites. Inspection request for [redacted] cancelled 9/30/02 by OC (S. Adams).
Pharm Tox	Impurities levels consult	6/24/02	Completed/LPei	Completed 8/28/02. Reviewer found the provided data are insufficient to support the safety of the degradant levels in the drug product.
Biopharm	N/A	N/A	N/A	No biopharm issues
LNC	Evaluation of Spiriva	2/22/02	Acceptable N. Roselle DMETS	none
Methods Validation	MV Package	-	Needs to be updated	Will be forwarded to FDA labs when updated
OPDRA				
EA	N/A	N/A	N/A	Applicant requested a Categorical Exclusion
Microbiology	N/A	N/A	N/A	No consult needed

The blisters consist of an aluminum based peeling foil, a polyvinylchloride forming film that is molded into separate cavities each holding a single capsule and an aluminum based protective bottom foil. The second element of the drug product is the HandiHaler device that enables extraction of the dose from the capsules and dispersion of the drug substance in the inhalation airstream of a patient. The Tiotropium Hard Capsules are single use only whereas the HandiHaler device is to be used repeatedly.

Drug Product-Related Issues:

1. [redacted] lactose monohydrate are present in the formulation. The lactose monohydrate in the formulation consists of [redacted] lactose.

2. [redacted]

3. The batch data show an [redacted] upon storage for [redacted]. The applicant has been requested to [redacted]

4. After filling [redacted]

5. No description of the [redacted] lactose monohydrate has been provided.

6. Packaging in the blisters is [redacted]

7. No Master Batch Record for manufacture of *Tiotropium Inhalation Powder, Hard Capsule 18µg* has been submitted. The applicant has been requested to provide one.

8. DMFs [redacted] have been reviewed and are considered inadequate to support this application.

9. The applicant has been requested to modify the design of the [redacted]

10. The formulation undergoes significant loss of emitted fine particles and emitted dose when exposed to the atmosphere for 24 hours. The applicant has disclosed that the losses are [redacted] To further investigate this situation, the applicant has been requested to provide data from any investigation of the use of alternative capsule materials.

11. As a result of the above problem, as well as degradation of the drug substance to [redacted], the applicant has been requested to provide the results of a study that demonstrate the maximum length of time that the drug product may be held outside of its protective packaging without resulting in a significant change in either emitted dose or particle size distribution. The above [redacted] is a degradant from [redacted]

12. No data has been provided on batch-to-batch variability in flow resistance through the HandiHaler. This has been requested.

13. Both the [redacted] methods utilize [redacted] through the instrument. The applicant has been asked to examine the [redacted]

14. The applicant has been asked to perform in-use studies of dose delivered to determine the frequency of cleaning and related instructions to be included in the labeling. They have provided data on cleaning, but it is from a study that does not take into account the 24-hour period between actuations as seen in patient usage.

15. The applicant expects the Handihaler to be used for [redacted] before replacement is required.

16. The stability protocol needs extensive additions to conform to the guidance recommendations.

17. No data has been provided on the stability of the drug product at 25°C/75% RH. This data is necessary to provide assurance of the overwrap quality with respect to the effect of moisture on particle size distribution.

18 CMC comments on the labeling are deferred until additional data are received.

B. Description of How the Drug Product is Intended to be Used

The drug product is intended to be used as a dry powder inhalation device and container closure. It is expected that patients will use the device to provide 10.4 µg of tiotropium once a day for long-term maintenance of COPD.

C. Basis for Not-Approval Recommendation

The application is deficient for drug substance and drug product manufacturing and specifications. It is also deficient for drug product stability and developmental studies.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

ChemistName/Date: Same date as draft review
ChemistryTeamLeaderName/Date
ProjectManagerName/Date

C. CC Block

210 Page(s) Withheld

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

/s/

Brian Rogers
11/20/02 11:55:03 AM
CHEMIST

Guiragos Poochikian
11/20/02 12:34:47 PM
CHEMIST

PHARMACOLOGY/TOXICOLOGY REVIEW FOR

CHEMISTRY CONSULTATION REQUEST

Review #2

Application Information	
NDA number:	21-395
Drug Name:	Tiotropium Bromide (dry powder inhalation capsules)
Sponsor and/or agent:	Beohringer Ingelheim Pharmaceutical Inc.
Date of submission:	July 31, 2003
Request Information	
Request Subject	Safety evaluation of tiotropium degradants
Request Initiator	Dr. Brian Rogers
Request Date	24-JUN-2002
Reviewer Information	
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
Division Code:	HFD-570
Review Completion Date:	December 8, 2003

SUMMARY: This review evaluates the adequacy of the 31-JUL-2003 submission addressing nonclinical qualification of degradants in the Spiriva Handihaler® application. The degradants are [redacted] The submission contains a recently completed 13-week inhalation toxicity study of [redacted] degradants [redacted] in rats. The study revealed no degradant treatment-related toxicities in the respiratory system. It, however, failed to achieve a significant pulmonary deposition of the degradants in rats. The highest pulmonary exposure of the degradant in rats was [redacted] ng/kg/day, which is approximately equal to the expected exposure levels in humans [redacted] ng/kg/day for [redacted] and [redacted] ng/kg/day for [redacted] respectively; these doses were calculated based on the newly proposed degradant specifications of [redacted] for [redacted] The study, therefore, is considered inadequate in qualifying the degradants because of the lack of an adequate safety margin. The review recommends retaining the previous recommendation of limiting each degradant at [redacted] The sponsor needs to provide additional preclinical data to demonstrate the safety of the degradant levels if they cannot comply with the recommendation.

REVIEW

Previous evaluations have identified the safety qualification of [redacted] degradants in Spiriva DPI as an outstanding nonclinical issue. The evaluations include reviews by Dr. Luqi Pei dated August 28, 2002 and September 17, 2002, and memoranda by Joseph Sun dated September 20, 2002 and by Dr. David Morse dated October 18, 2002. The degradants are [redacted] These reviews conclude that the sponsor has not conducted necessary nonclinical studies to qualify

up to — the degradants in drug product that exceeds the ICH qualification threshold of 1.0%.

Currently, the sponsor proposes the following specifications for the degradants: —

— These specifications (except for — exceed the ICH qualification threshold, but are almost identical to that that in the Division's approvable letter dated December 30, 2002 — The action letter used the specifications from Dr. Brian Rogers' CMC review.

The newly proposed specifications, however, differ from the previous nonclinical recommendation although they are almost in compliance with the action letter. The new specifications are also lower than the originally proposed specifications of up to — for each degradant. The nonclinical discipline previously recommended specifications of less than 1.0% for each degradant. This recommendation was faxed to the sponsor on October 25, 2002. The fax states:

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

The above nonclinical recommendations were from Dr. Luqi Pei's review dated August 28, 2002. Dr. Pei's review was generated in response to a Chemistry Consultation Request by Dr. Rogers on June 24, 2002. There are apparent discrepancies between the chemistry and nonclinical recommendations. These discrepancies prompted internal discussions of the application by the review team on November 6 and 7, 2003. The team concluded that the specifications should be set based on the nonclinical information.

Degradant — is no longer considered an outstanding issue. The current proposed specification for — is not-more-than 1% (page 2 of the cover letter). — — The specification for — is considered acceptable because it is in compliance with the ICH qualification threshold. The following discussion addresses — degradants: —

Historical Perspective

Retrospectively, the Division and BI have held several discussions on the qualification of the degradants. Table 1 (next page) summarizes major events during the discussion. The Division considers this an impurity/degradant issue and subject to the ICH Q3B guidance on qualification of drug product impurities. The Division's determination was documented in Dr. Pei's review for Chemistry Consultation Request dated August 28, 2002.

BI's position on the issue —

Table 1. Major Events in Qualification of Spiriva Handihaler® Degradants

Date	Event Description
12-MAY-1999	Pre-NDA meeting was held; safety qualification of the degradants was discussed.
21-DEC-2001	BI Filed the Spiriva NDA.
March, 2002	BI initiated a 13-week inhalation toxicity study of the degradants in rats (Document N. U03-1175) without informing the Division.
28-AUG-2002	Dr. L. Pei completed the review of the qualification data in the DNA and concluded the data were insufficient to support proposed specifications.
25-OCT-2002	Division informed the sponsor of the deficiencies via fax and recommended a 13-week inhalation toxicity study in one animal species as a remedy.
30-DEC-2002	Division issued the approvable action letter and set acceptable specifications for the degradants.
02-FEB-2003	BI finalized the report for study U03-1175, again without informing the Agency.
14-MAR-2003	BI submitted a protocol for the already completed study (Study U03-1175) and requested Division's comments on the protocol.
01-APR-2003	Division initiated a telecon to discuss the protocol; BI revealed that Study U03-1175 had been completed. Division conveyed no comments.
12-NOV-2003	Dr. Pei completed the review of the 13-week inhalation toxicity study in rats under IND 46,687.

BI completed genetic toxicity testing and general toxicity studies of the degradants prior to the pre-NDA meeting. BI also voluntarily initiated a 13-week inhalation toxicity study of the degradants in rats when the application was in the first review cycle. This study coincides with the Division's later recommendation as discussed later, but was initiated prior to the Agency's comment on the issue. BI, however, did not inform the Agency of this study until the study was completed.

Major nonclinical discussions between the Division and BI on the degradant qualification issue are documented in minutes of the 19-MAY-1999 pre-NDA meeting and of the 25-OCT-2002 and 01-APR-2003 telephone conferences. Two other relevant documents are Dr.

Pei's review for chemistry consultation request dated August 28, 2002 and the sponsor's summary on impurities in the original NDA submission (vol. 1, p 104-109). In July 2003, the sponsor and the Division finally agreed to classify these compounds as degradants. Both sides also agreed that a 13-week inhalation toxicity study of the degradants in rats was needed to qualify the degradant levels. BI completed a 13-week inhalation toxicity study of the degradants in rats.(Document No. U03-1175). This study will be discussed later in the section of Summary of Relevant Nonclinical Data.

Summary of Relevant Nonclinical Data

BI conducted genetic toxicity testing of these degradants (two assays for each degradant) and general toxicity studies with the treatment durations up to 13 weeks. Dr. Pei reviewed the genetic toxicity studies and general toxicity studies up to 4 weeks in a review dated August 28, 2002. None of the degradants were genotoxic under the testing conditions. In a 4-week inhalation toxicity study, degradant doses (pulmonary) were — ng/kg/day for — and — ng/kg/day for — No degradant treatment-related toxicity was found.

As indicated previously, BI also completed the required 13-week inhalation toxicity study of the degradants in rats (Document No. U03-1175). The study, however, was completed without the Division's input on the protocol of the study. BI initiated the study in March 2002, completed it in December 2002, and finalized its report on February 8, 2003. On March 14, 2003, BI submitted a protocol and requested Division's comments on the protocol, although BI indicated that the study was ongoing in the submission. On April 1, 2003, the Division initiated a telephone conference to discuss the protocol. In the telephone conference, BI finally revealed that the study had been completed. The Division deemed it unnecessary to comment on the protocol.

Dr. Pei recently reviewed the 13-week inhalation toxicity study in rats [Study No. U03-1175, see the review dated 12-NOV-2003 (note final electronic sign-off date in DFS is 12/1/03) in IND 46,687]. Briefly, Wistar rats (10/sex/group) were exposed nose-only to aqueous aerosols of tiotropium in the presence or absence of its degradants for 90 days. The degradant were — One group received tiotropium alone. Four groups received tiotropium plus one of the degradants. Another group received tiotropium plus — and — Another group received tiotropium — The last group received only vehicle that contained unspecified amounts of benzalkonium chloride and EDTA. Concentrations of the degradant ranged between — , of tiotropium when used in combination or alone, respectively. The duration of exposure was 60 minutes/day. The mean mass aerodynamic diameter (MMAD) was approximately — Tiotropium doses were approximately 20 and 0.3 µg/kg/day for the total inhaled (range: 20 – 22 µg/kg/day) and pulmonary deposition (range: 0.3 – 0.33 µg/kg/day based on 1.5% pulmonary deposition), respectively. The inhaled degradant doses were approximately — µg/kg/day when only one degradant was present and — µg/kg/day for each degradant when two were present. These doses were based on the aerosols with aerodynamic diameters of — The pulmonary doses of the degradants, however, were only — µg/kg/day when only one degradant was present and —

ng/kg/day for each degradant when two were present. This was based on a pulmonary deposition efficiency of — for particles with MMAD of —

The results showed that the presence of the degradants (— did not change significantly the toxicity profile of tiotropium. There were no significant differences in body weight or body weight gains in rats receiving tiotropium or tiotropium plus degradants. Neither was there any difference in the incidences of microscopic lesions. Microscopic lesions were concentrated in the nasal turbinates and larynx. In the nasal turbinates, increased incidences of squamous metaplasia of the transitional epithelium were observed all rats receiving tiotropium only or tiotropium plus the degradant. Also observed were the increased incidences of squamous hyperplasia of the respiratory epithelium and subepithelial infiltration of inflammation cells in the male rats. In the larynx, increased incidences of slight necrosis of ventral cartilage and epithelial hyperplasia and keratinization were observed in both sexes. The lack of remarkable differences among the tiotropium and tiotropium plus degradants suggests that the presence of the degradant in the tiotropium, either alone or in combination with another degradant, do not cause additional toxicity in rats.

Evaluation

The newly completed 13-week inhalation toxicity study of the degradant in rats revealed no degradant treatment-related toxicities, either alone or in combination with another degradant. Unfortunately, the study fails to provide sufficient safety margins to support the newly proposed specifications of
The highest pulmonary exposure of each degradant in rats was approximately — kg/day. The expected human exposure of each degradant is — ng/kg/day (based on specifications of — and — degradants), respectively. The safety margins were approximately 1 (Table 2).

Table 2. Safety Margins of Tiotropium Degradants in the Spiriva HandiHaler

Impurity	Clinical Form. Specification		Preclinical Data Preclinical dose		Species	Duration (week)	Route	Safety Margin [d]
	%	ng/kg	%	(ng/kg) [c]				
—	—				Rat	13	IH	1.1
	—				Rat	13	IH	1.1
	—				Rat	13	IH	1.6

a. Maximum clinical dose at — level: (— The calculation for — is identical to that of —

b. Maximum clinical dose at — level: (

c. Preclinical dose: —

d. Safety margin = preclinical dose (— kg/day) ÷ clinical dose — /day or — /day) = 1.1 or 1.6.

The lack of a sufficient safety margin (approximately 1) renders the study inadequate to qualify the impurity levels. Thus, the previous recommended specification of — or — for each degradant remains applicable. Additional

information is needed should the sponsor be unable to comply with these specifications. The additional information includes a demonstration of sufficient margin of safety between animals and humans regarding the pulmonary exposure of the degradants in Study U03-1175 or other studies. Should the response be deemed unsatisfactory, another 13-week inhalation toxicity study of the degradants in one animal species must be conducted.

The sponsor also needs to clarify the difference in tiotropium toxicity between the current study (U03-1175) and previously completed studies (U03-1175, U091-493 and U093-0945) in the same strain of rats (Wistar). As discussed in Dr. Pei's review dated November 12, 2003 (electronic sign off date of 01-DEC-2003) in IND 46,687, Study No. U03-1175 showed more severe and prevalent tiotropium-related lesions in the respiratory tract in rats. In the current study, metaplasia, hyperplasia and inflammation were observed in every tiotropium-treated rat group. The lesion is much more severe than the previous studies. It is unclear why such a remarkable difference existed among the studies. The sponsor needs to clarify the difference. Although the increased incidence of tiotropium-related toxicity observed in Study U03-1175 is not directly relevant to the impurity qualification, the issue should be clarified should the sponsor attempt to show that this study is adequate to qualify the impurities since it does bring into question the overall validity of the study.

Conclusion:

The proposed specification of NMT 1% for — in the drug product is acceptable as it conforms to ICH recommendations.

The sponsor has not provided adequate nonclinical data to qualify the proposed drug product impurity levels: — The previous recommendation of specifications of NMT 1% for — each remains applicable. Additional information is needed should the sponsor be unable to comply with these specifications. The additional information includes:

1. Demonstration of sufficient margin of safety between animals and humans regarding the pulmonary exposure of the degradants in Study U03-1175. This could be achieved by examining the particle size distribution curve of the study and corresponding deposition fractions. At present, it is unclear whether the sponsor has considered this factor.
2. A 13-week inhalation toxicity study of the degradants in one animal species if study U03-1175 fails to provide sufficient safety margin between animals and humans regarding pulmonary exposure. Pulmonary deposited doses should be selected to provide an adequate margin of safety in comparison to the maximum expected clinical dose.

Recommendation

Specifications for each of the — iotropium degradants — in Spiriva HandiHaler® Capsule should be set at not-more-than 1.0%. Additional information is needed should the sponsor be unable to comply with these specifications. The additional information includes:

1. Demonstration of sufficient margin of safety between animals and humans regarding the pulmonary exposure of the degradants in Study U03-1175.

2. A 13-week inhalation toxicity study of the degradants in one animal species if study U03-1175 fails to provide a sufficient safety margin between animals and humans regarding pulmonary exposure. Pulmonary deposited doses should be selected to provide an adequate margin of safety in comparison to the maximum expected clinical dose at the proposed drug product specifications.

Luqi Pei, Ph.D.	Timothy McGovern, Ph.D.
Pharmacologist	Supervisory Pharmacologist

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/s/

Luqi Pei
12/8/03 01:29:25 PM
PHARMACOLOGIST

Timothy McGovern
12/8/03 02:00:28 PM
PHARMACOLOGIST
I concur.

PHARMACOLOGY AND TOXICOLOGY REVIEW FOR

CHEMISTRY CONSULT REQUEST

Application Information

NDA number:	21-395
Drug Name:	Spiriva HandiHaler (tiotropium bromide)
Sponsor and/or agent:	Boehringer Ingelheim
Date of submission:	July 31, 2003

Request Information:

Request Initiator:	Alan Schroeder, Ph.D.
Request Date:	October 21, 2003
Subject:	Safety evaluation of foreign particulates

Reviewer Information

Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
Division Code:	HFD-570
Review Completion Date:	November 17, 2003

REVIEW

The proposed specification for foreign particulates in the Spiriva Handihaler (below) is acceptable, but should be tightened down to reflect the actual CMC data. In an Email message dated 21-OCT-2003, Dr. Alan Schroeder requested a nonclinical safety evaluation of the following proposed specifications for the particulate in the Spiriva application (Appendix):

Particle Size	Max. Number of Particles Per Capsule
<	
≥	
≥	

The estimated exposure of the particulate is μg/kg/day. Dr. Schroeder estimates that the maximum daily exposure of the particulate, at worst scenario, is μg particulates/capsule. Spiriva is to be used one capsule per day. For a 50-kg patient, this corresponds to a daily dose of μg/kg/day (g = g/kg/day).

The exposure of μg/kg/day of particulates is considered safe. The content of the Spiriva capsule consists of tiotropium, lactose and
The safety of has been well established but the composition of the particulates is unknown. Dr. Schroeder, the chemistry reviewer, states that "The

preponderance (e.g., [redacted] of particles were shown by [redacted] to be consistent with organic matter. 'The morphology for these particles varied and they could not be uniquely identified in most cases, although some showed [redacted]" Dr. Craig Bertha (Acting Chemistry Team Leader, personal communication) indicates that, there is no evidence to suggest, neither is there reason to suspect, the presence of particularly obnoxious compounds in the particulate. Thus, it is reasonable to apply the EPA's standard for particulates for the safety evaluation of the Spiriva application. The EPAs standards for unknown nuisance particulates with aerodiameters of 2.5 ($PM_{2.5}$) and 10 (PM_{10}) μm is 15 and 50 $\mu g/m^3$, respectively. They correspond to a daily dose of 6 and 20 μg/kg/day of foreign particulates, based on a daily breathing air volume of 20 m^3 for a 50-kg individual. The 24-hr PM_{10} value is even higher (150 $\mu g/m^3$). Of these standards, $PM_{2.5}$ is the most conservative and can be applied to evaluate the safety of the foreign particular matters of this application. The maximum exposure of the particulate from Spiriva [redacted] μg/kg/day) is below the EPA standard of 6 μg/kg/day for $PM_{2.5}$. Thus, the safety of the particulate in the Spiriva application is considered qualified. However, it is recommended that the sponsor tighten down the specification to reflect the actual CMC data. This would minimize any potential adverse effect associated with the particulate.

Conclusion:
The specification of the particulate in the Spiriva application is acceptable, but it is recommended to tighten down the specification to reflect the actual CMC data.

Luqi Pei, Ph.D.
Pharmacologist

Timothy McGovern, Ph.D.
Supervisory Pharmacologist

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/s/

Luqi Pei
11/17/03 03:18:17 PM
PHARMACOLOGIST

Timothy McGovern
11/18/03 07:53:27 AM
PHARMACOLOGIST
I concur.

PHARMACOLOGY/TOXICOLOGY REVIEW

FOR

CHEMISTRY CONSULT REQUEST

Application Information	
NDA number:	21-395
Drug Name:	Tiotropium Bromide (dry powder inhalation capsules)
Sponsor and/or agent:	Beohringer Ingelheim Pharmaceutical Inc.
Date of submission:	December 12, 2001 and July 25, 2002
Request Information	
Request Subject	Safety evaluation of tiotropium degradants
Request Initiator	Dr. Brian Rogers
Request Date	24-JUN-2002
Reviewer Information	
Reviewer Name:	Luqi Pei, Ph.D.
Division Name:	Pulmonary and Allergy Drug Products
Division Code:	HFD-570
Review Completion Date:	August 28, 2002

SUMMARY

This review evaluates the safety of tiotropium impurities and degradants: up to will be present in the drug substance and the remaining degradants (up to each) will be present in the drug product. Data supporting the specifications are genetic and general toxicity studies of the degradants. At least two genetic toxicology assays have been completed for each degradant and no evidence of genotoxicity is revealed. Also completed are a 13-week inhalation study for and a four-week inhalation toxicity study of tiotropium spiked with the proposed concentrations of n rats. No remarkable findings were revealed in either study. No repeat-dose inhalation toxicity study is available for these data are insufficient to support the safety of the level of the degradants in the tiotropium product. The sponsor should provide additional preclinical data to demonstrate the safety of the degradant levels.

REVIEW

I. INTRODUCTION

This review is generated in response to a Chemistry Consult Request initiated by Dr. Brain Rogers, the Chemistry Reviewer for the application, on June 24, 2002. Dr. Rogers requested a preclinical safety review of impurities and/or drug degradation products of tiotropium bromide. For the convenience of discussion, the review simply refers them as degradants. Table 1 lists degradants in the tiotropium drug substance and product that are of safety concern. These degradants are The criteria for determining whether a degradant is of safety concern are the ICH qualification threshold levels of not-more-than (NMT) 0.1% for the drug substance and NMT 1.0% for the drug product respectively.

Table 1. Degradants Levels in Tiotropium Drug Substance and Product

Impurity	Degradant Level (Not More Than %)		
		Drug Product	
	Drug Substance	Time of Release	Shelf Life

a. The sum may be NMT

To support the safety of the degradants in their product, the sponsor has completed ten genetic toxicity testing, several acute toxicity studies and two repeat-dose toxicity studies of the degradants. These studies are submitted in the NDA (Table 2).

[1] This review uses the code names only. The application uses two naming systems the degradants. Its metabolism studies use chemical names while stability studies use code names. Consequently, different names are used to refer to the same compound. Examples are Some study reports even use different code names for the same compound (i.e To simplify the discussion, the review uses only one code name for each compound.

Table 2. Toxicology Studies of Tiotropium Degradants

Study Description	Report #	Vol./p
Genetic Toxicology Studies		
[redacted] unscheduled DNA synthesis test (UDS) in rat hepatocytes *in vitro*	U91-0636	57
[redacted] point mutation testing in Salmonellatyphimurium and Escherichia coli assay	U92-0474	56
[redacted] Mouse bone marrow micronucleus test (IV)	U98-2246	57
[redacted] - Testing for point-mutagenic activity with salmonella typhimurium	U92-0498	56
Point-mutagenicity study in Salmonella typhimurium of [redacted]	U92-0074	56
Micronucleus assay of [redacted]	U99-1477	56
Micronucleus assay of [redacted]	U99-1478	56
Micronucleus assay of [redacted] after repeated inhalation	U99-1565	56
Mutagenicity study with [redacted] in the *S. typhimurium*/ mammalian microsome assay (Ames test)	U99-1650	56
Chromosomal aberrations in human lymphocytes with [redacted] *in vitro*	U99-1651	56
General Toxicity Studies[a]		
[redacted] Acute oral and intravenous toxicity studies in mice	U92-0584	54
[redacted] aqueous solution) 13 week inhalation toxicity study in rats	U97-2187	54
4 week inhalation toxicity study of tiotropium bromide and degradation products [redacted] in rats	U00-1104	53

a. The table does not include the previously submitted and reviewed acute toxicity studies of the degradants.

II. GENETIC TOXICITY STUDIES

1. **Study Title: Point-mutagenicity study in *Salmonella typhimurium* of [redacted] (Study U92-0074)**

2. **Study Title: [redacted] - Testing for point-mutagenic activity with *salmonella typhimurium***

Dr. Satish Thipathi reviewed the above two studies in a review dated 26-AUG-1996 under IND 46,687. No evidence of genotoxicity was found.

3. **Study title: Mutagenicity Study on [redacted] in the *in vitro* Rat Hepatocyte: UDS**

Key findings: [redacted] did not cause genetic damage in the rat UDS assay under the testing conditions.

Study no: U91-0636
Study type (if not reflected in title): *in vitro* UDS Test of [redacted] in Rat Hepatocytes
Volume #, and page #: Vol. 57
Conducting laboratory and location: Beohringer Ingelheim, Dr. [redacted] GmbH, Department of Experimental Pathology and Toxicology, 7950 Biberach.
Date of study initiation: December 17, 1990; end: March 28, 1991
GLP compliance: yes

QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch B

Formulation/vehicle: water/Williams' Medium E

Methods:

Strains/species/cell line: Primary rat [Chbb:THOM9SPF] hepatocytes
Dose selection criteria:
Basis of dose selection: ICH limit concentration (up to 5,000 µg/ml) and toxicity
Range finding studies: No.
Test agent stability: stable
Metabolic activation system: N/A
Controls:
Vehicle: water
Negative controls: the culture medium
Positive controls: 2-acetylamineofluorene
Comments: None
Exposure conditions:
Incubation and sampling times: A mono-layer culture of freshly prepared rat hepatocytes from 100,000 cells were fed with 2 ml medium containing 20 µl of 3H-thymidine (10 µCi). The cells were treated with different concentrations of [redacted] for 18 hours. They were then washed with phosphate buffer, fixed in ethanol/acetic acid and air-dried. After being developed at 4°C for 7 days, the preparation was then stained with hematoxyline before analysis.
Doses used in definitive study: 20, 100, 500, 1,000, 2,500 and 5000 µg/ml
Study design: The ability of [redacted] to induce net grain formation (NDA fragment unincorporated in to chromosomes) was evaluated in the presence and absence of the enzyme activation system. Six [redacted] concentrations (20 – 5000 µg/ml) were used. Both negative and positive controls were included. Two independent studies were performed. Mean net grains (nucleus gains minus cytoplasmic grains) were estimated from three areas of 20 morphologically unaltered cells.
Analysis: No statistical analysis was performed.
Number of replicates: 3
Counting method: automatic counter ([redacted] onnected to a video camera
Criteria for positive results: Mean net grain count is ≥ 5 for any dose is consider positive. The mean net grain count of 1 – 4 was considered equivocal or weakly positive.

Results:

Study validity: This study is valid. Both the positive and negative controls showed expected results.
Study outcome: [redacted] tested negative in the rat UDS assay. A slight increase in net grain counts (0.5 – 1.4) was observed in the mid concentrations (1000 and 2500 µg/ml) of the first experiment. The finding, however, was not confirmed in the repeat confirmation test. The slight increase in the net grains in the mid doses, thus, are not considered treatment related. The positive control produced significant increases in net grains (mean = 18) in both experiments.

Clastogenicity of [redacted] was evaluated in a mouse micronucleus assay. Mice (5/sex/treatment) were given intravenously [redacted] mg/kg of [redacted] or 30 mg/kg of cyclophosphamide. Bone marrow was collected 24 hours later and analyzed for the number of micronucleated polychromatic erythrocytes (MPCE). [redacted] did not cause an increase in the number of MPCE, nor did it increase in PCE/NCE ratio. The frequency of MPCE ranged 0-0.3%, 0-0.25% and 1.5-2.45% for the vehicle control, [redacted] and the positive control, respectively. The value of the vehicle control and [redacted] are within the normal range of the testing lab. The value of the positive control is statistically significantly different from the control ($p < 0.05$).

4. Study title: [redacted] **Test for Point Mutagenic Activity with *Salmonella typhimurium* and *Escherichia coli***

Key findings: No evidence of mutagenicity of [redacted] was found.

Study no: U92-0474
Volume #, and page #: Vol. 57
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology, D-6507 Ingeiheim.
Date of study initiation: 25-FEB-1992; end: 27-MAR-1992
GLP compliance: yes
QA reports: yes (x), no ( )
Drug, lot #, radiolabel, and % purity: Batch A1, 101.7% purity, expiration on August 1993

Formulation/vehicle: Aqueous solution

Methods:

Strains/species/cell line: *S. typhimurium:* TA 98, TA 100, TA 1535, TA 1537, TA 1538; *E. coli:* WP2uvrA
Dose selection criteria:
Basis of dose selection: 1983 OCED guidelines (5,000 µg/plate)
Range finding studies: No.
Test agent stability: stable
Metabolic activation system: liver fractions from rats treated with 500 mg/kg of Aroclor 1254 for five days
Controls:
Vehicle: water/ DMSO
Negative controls: the culture medium
Positive controls: 2-aminoanthracene, 1-ethyl-3-nitro-1-nitrosoguanidine, 1-methyl-3-nitro-1-nitrosoguanidine, 2-nitrofluorene,
Comments: None
Exposure conditions:

Incubation and sampling times: Agar containing bacteria and the test material was incubated at 37°C for 48 hours.

Doses used in definitive study: 10, 100, 500, 1,500 and 5,000 µg/plate

Study design: The ability of — to induce an increase in revertant colonies (result of point mutation) was evaluated in the Ames test in the absence and presence of the enzyme activation system. The study used five — concentrations, and the appropriate positive and negative controls.

Analysis: The number of revertant colonies.

Number of replicates: 3

Counting method: unspecified

Criteria for positive results: unspecified.

Results:

Study validity: This study is valid.

Study outcome: No remarkable findings. The — treatment did not cause any apparent increase in the number of revertant colonies over the negative controls. The positive controls did produce marked increase in the number of revertant colonies.

Study Summary:

The mutagenic potential of — was evaluated in the Ames test. *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and *E. coli* WP2uvrA were treated with — at concentrations of 10 – 5,000 µg/plate. The number of revertant colonies was counted and compared against the negative and positive controls. The positive control produced remarkable increases in the number of revertant colonies over the negative controls. The — treated cells did not show any increase in the number of revertant colonies over the negative control.

5. **Study title:** — **Mouse Bone Marrow Micronucleus Test after Intravenous Administration**

Key findings: No evidence of — clastogenicity was found.

Study no: U98-2246
Volume #, and page #: Vol. 57
Conducting laboratory and location: Beohringer Ingelheim, Dr. — GmbH, Department of Experimental Pathology and Toxicology,
Date of study initiation: 05-JUL-1995; End: 22-JUN-1995
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch I, 99.9% purity, expired in November 1995

Formulation/vehicle: saline

Methods:

Strains/species/cell line: Mice [Ico:OF1(IOPS Caw)]

Dose selection criteria:

Basis of dose selection: the maximum tolerated dose or minimal lethal dose.

Range finding studies: yes. An early dose ranging study showed that [redacted] at doses of 10 mg/kg and above was lethal to mice (Table 3).

Table 3. Mortality of [redacted] in a Dose Ranging Study

	[redacted] (mg/kg)				
	6	8	10	12.5	15
Male	0/4	0/3	1/5	1/4	1/1
Female	0/4	0/3	0/4	1/4	-

Test agent stability: stable

Metabolic activation system: N/A

Controls:

Vehicle: Saline

Negative controls: saline

Positive controls: cyclophosphamide (30 mg/kg)

Comments: None

Exposure conditions:

Incubation and sampling times: Bone marrow samples were collected 24 and 48 hours after treatment. The sample was fixed with absolute methanol and stained with acrifine orange solution.

Doses used in definitive study: 2.5, 6 and 10 mg/kg [redacted], via tail vein in an injection volume of 10 ml/kg.

Study design:

The clastogenicity of [redacted] was evaluated for its ability to induce micronucleus formation in bone marrow erythrocytes in male mice. Table 4 shows the study design.

Table 4. Design of the Mouse Micronucleus Test of [redacted]

		Number of Blood Samples	
	Dose (mg/kg)	24 hr	48 hr
Saline		5M, 5F	-
[redacted]	2.5	5M	-
	6	5M	-
	10	5M, 5F	5M, 5F
Cyclophosphamide	30	5M, 5F	-

Analysis: the frequency of micronucleated polychromatic erythrocytes (MPCE) and the ratio of polychromatic erythrocytes (PCE) and normochromatic erythrocytes (NCE). Statistical analysis was the Fisher-Pitman test.

Number of replicates: 2 (1/femur)

Counting method: [redacted]

Color was used to distinguish cells:

PCE: orange to bright red

NCE: dark or almost dark surrounded by a greenish ring

Micronuclei: Pale green/pale yellow.
Two thousand erythrocytes were counted per animal.

Results:

Study validity: valid.

Study outcome: — did not cause an increase in the frequency of MPCE, nor did it increase in PCE/NCE ratio. The frequency of MPCE ranged 0-0.3%, 0-0.25% and 1.5-2.45% for the vehicle control, — and the positive control, respectively. The value of the vehicle control and — are within the normal range of the testing lab. The value of the positive control is statistically significantly different from the control ($p < 0.05$).

Study Summary:

The clastogenicity of — was evaluated in a mouse micronucleus assay. Mice (5/sex/treatment) were given intravenously 0, 2.5, 6 or 10 mg/kg of — or 30 mg/kg of cyclophosphamide. Bone marrow was collected 24 hours later and analyzed for the number of micronucleated polychromatic erythrocytes (MPCE). — did not cause an increase in the number of MPCE, nor did it increase in PCE/NCE ratio. The frequency of MPCE ranged 0-0.3%, 0-0.25% and 1.5-2.45% for the vehicle control, —, and the positive control, respectively. The value of the vehicle control and — are within the normal range of the testing lab. The value of the positive control is statistically significantly different from the control ($p < 0.05$). — is considered non-clastogenic under the testing conditions.

6. Study title: Mutagenicity Study in the Mouse Bone Marrow Micronucleus Assay after Intravenous Treatment with — degradation product of Ba 679 BR)

Key findings: No evidence of — clastogenicity was found.

Study no: U99-1477
Volume #, and page #: Vol. 56
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology,
Date of study initiation: 07-Jun-1999; ended on 16-Jun-1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch I, expired in Dec. 1999

Formulation/vehicle: saline

Methods:

Strains/species/cell line: male mice [NMRI]
Dose selection criteria:
Basis of dose selection: 1997 OECD and ICH guidelines.
Range finding studies: yes. A single dose of 100 mg/kg of — resulted in (2) mortality during the injection. The high dose was two-thirds of the lethal dose.

Because of the similarity of LD_{50} between male (145 mg/kg) and females (168 mg/kg), only male was used for the study.

Test agent stability: stable

Metabolic activation system: N/A

Controls:

Vehicle: Saline

Negative controls: saline

Positive controls: cyclophosphamide (20 mg/kg)

Comments: It can be argued that the study should use the

Exposure conditions:

Incubation and sampling times: Bone marrow samples were collected 24 hours after treatment. The sample was stained with May-Grunwald/Giemsa.

Doses used in definitive study: 10, 30 and 60 mg/kg — in 10 ml/kg injection volume (tail vein)

Study design: Five male mice per treatment were given intravenously saline; 10, 30 and 60 mg/kg of —; and 20 mg/kg of cyclophosphamide. The percentage of MPCE in bone marrow between groups was compared.

Analysis: percentage of MPCE between groups. The Fisher-Pitman permutation test was used. Criteria for a positive result is a statistically significant, dose-dependent increase in the frequency of MPCE in the treatment groups.

Number of replicates: None

Counting method: Unspecified. Micronuclei are defined as darkly stained and generally round nuclear bodies between 1/10 and 1/5 of the size of polychormatic erythrocytes (NCE). Two thousand erythrocytes per animal were analyzed for the incidence of micronuclei and 200 cells per slide were used to determine the ratio of PCE and NCE.

Results:

Study validity:

Study outcome: No increase in the frequency of MPCE was observed in the — treatment groups. The percentage of MPCE was 0.14% for the vehicle-control group, 0.18-0.21% for the — treatment groups, and 1.91% for the positive control, respectively. There was no significant difference in the ratio of PCE to NCE among the group (52.5% - 60.7%). No remarkable treatment-related clinical signs were observed with the exception of one of five high dose animals exhibiting convulsion two minutes after dosing.

Study Summary:

Mice (5/sex/treatment) were given intravenously 0, 10, 30, 60 mg/kg of —, or 20 mg/kg of cyclophosphamide. Bone marrow was collected 24 hours later and analyzed for the number of micronucleated polychromatic erythrocytes (MPCE). — did not cause any increase in the number of MPCE, nor did it increase in PCE/NCE ratio. The frequency of MPCE was 0.14%, 0.18–0.25% and 1.91% for the vehicle control, — and the positive control, respectively. The value of the positive control is statistically significantly different from the control ($p < 0.05$). No evidence of — clastogenicity was found.

7. Study title: Mutagenicity Study in the Mouse Bone Marrow Micronucleus Assay after Intravenous Treatment with [redacted] (degradation product of Ba 679 BR)

Key findings: No evidence of [redacted] clastogenicity was found.

Study no: U99-1478
Volume #, and page #: Vol. 56
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology,
Date of study initiation: 07-Jun-1999; ended on 15-Jun-1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch I, expired in Dec. 1999

Formulation/vehicle: saline

Methods:

Strains/species/cell line: male mice [NMRI]
Dose selection criteria:
Basis of dose selection: 1997 OECD and ICH guidelines.
Range finding studies: yes. Mice (2/dose) showed decreased motor activity and sedation after receiving 1000 and 2000 mg/kg of [redacted]
Test agent stability: stable
Metabolic activation system: N/A
Controls:
Vehicle: Saline
Negative controls: saline
Positive controls: cyclophosphamide (20 mg/kg)
Comments: none
Exposure conditions:
Incubation and sampling times: Bone marrow samples were collected 24 hours after treatment. The sample was stained with May-Grunwald/Giemsa.
Doses used in definitive study: 100, 300 and 1000 mg/kg [redacted] in aninjection volume 10 ml/kg (tail vein). Each animal was treated twice (24 hr apart) and was sacrificed 24 hours after the second dose.
Study design: Five male mice per treatment were given intravenously saline; 100, 300 and 1,000 mg/kg of [redacted] and 20 mg/kg of cyclophosphamide. The percentage of MPCE in bone marrow between groups was compared.

Analysis: percentage of MPCE between groups. The Fisher-Pitman permutation test was used. Criteria for a positive result is a statistically significant, dose-dependent increase in the frequency of MPCE in the treatment groups.
Number of replicates: None

Counting method: Counting MPCE and NCE. Two thousand erythrocytes per animal were analyzed for the incidence of micronuclei and 200 cells per slide were used to determine the ratio of PCE and NCE.

Results:

Study validity: It cab be argued that the top dose be increased. The high dose animal (1000 mg/kg/day for 2 days) showed only minimal signs of toxicity as decreased motor activity, half-closed eyes, and piloerection occurred up to two hours after the first injection.

Study outcome: No increase in the frequency of MPCE was observed in the [redacted] treatment groups. The percentage of MPCE was 0.14% for the vehicle-control group, 0.18-0.32% for the [redacted] treatment groups, and 1.91% for the positive control, respectively. There was no significant difference in the ratio of PCE to NCE among the group (57.1 – 62.5%).

Study Summary:

The clastogenicity of [redacted] was evaluated in a moue micronucleus assay. Mice (5/sex/treatment) were given intravenously 0, 100, 300 or 1,000 mg/kg of [redacted] or 20 mg/kg of cyclophosphamide. Bone marrow was collected 24 hours later and analyzed for the number of micronucleated polychromatic erythrocytes (MPCE). [redacted] did not cause an increase in the number of MPCE, nor did it increase in PCE/NCE ratio. The frequency of MPCE ranged 0.14%, 0.18-0.32% and 1.91% for the vehicle control, [redacted] and the positive control, respectively. The value of the positive control was statistically significantly different from the control ($p < 0.05$). No evidence of [redacted] clastogenicity was found.

8. Study title: **Mutagenicity Study in the Rat Bone Marrow Micronucleus Assay after Repeated Inhalation of Ba 679 BR Spiked with Its Degradation Products:** [redacted]

Note: This study is a part of the 4-week inhalation toxicity (Study U00-1104) assessing the toxicity of tiotropium and its degradation products. See the review of Study U00-1104 in the General Toxicology Section for details in study design.

Key findings: No evidence of clastogenicity of tiotropium spiked with degradants was found.

Study no: U99-1565
Volume #, and page #: Vol. 56
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology,
Date of study initiation: 27-FEB-1998; ended on 30-MAR-1998
GLP compliance: yes

QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: See Study U00-1104 of

Formulation/vehicle: See Study U00-1104 of General Toxicology Section

Methods:

Strains/species/cell line: 5 rats/sex/treatment [Chbb:THOM (SPF)]
Dose selection criteria:
Basis of dose selection: MTD in 4-week toxicity study; the report also states that the high dose is 50 times the human therapeutic dose.
Range finding studies: No.
Test agent stability: stable
Metabolic activation system: N/A
Controls:
Vehicle: 0.01% benzalkonium chloride and 0.05% EDTA.
Negative controls: None
Positive controls: None
Comments: This study lacks the positive control because it is a part of a repeat-dose general toxicity study that usually does not use positive control. The reason is that the safety concerns to the operating personals and the environment made using highly genotoxic compounds in repeat-dose inhalation studies impratical. On the other hand, the significance of such a study is unknown although the results (see later) indicated that there was difference in the frequency of PMCE between the treatment and negative (vehicle) controls and both values were within the historical range, especially with regard to the safety evaluation of the degradants.
Exposure conditions:
Incubation and sampling times: Bone marrow samples were collected 24 hours after treatment. Slides were made and stained with May-Grunwald/Giemsa.
Doses used in definitive study: Tiotropium doses: 0, 1.31 and 1.38 µg/kg/day tiotropium (estimated based on a pulmonary deposition factor of 0.07 and the achieved total inhaltion dose of 18.7 and 19.8 µg/kg/day, respectively). See Study U00-1104 for doses of the impurities.
Study design: Ability of tiotropium and its degradation products to produce chromosomal damage was assessed after an exposure period of 4 weeks to tiotropium and its degradation products. Slides were made from the bone marrow (5 rats /sex/treatment) collected 24-30 hr after the last dosing. The frequency of MPCE was compared among groups: the vehicle, tiotropium alone, and tiotropium spiked with the degradation products.

Analysis: The percentage of MPCE between groups. The Fisher-Pitman permutation test was used. Criteria for a positive result is a statistically significant, dose-dependent increase in the frequency of MPCE in the treatment groups.
Number of replicates: None

Counting method: Two thousand erythrocytes per animal were analyzed for the incidence of micronuclei and 200 cells per slide were used to determine the ratio of PCE and NCE.

Results:

Study validity: Validity is unknown.

Study outcome: Tiotropium spiked with — degradants did not cause any increase in the frequency of PMCE in rats. The frequency of MPCE was similar between the vehicle control (0.23%) and tropium-treatment groups (0.24 – 0.25%). There was no significant difference in the ratio of PCE to NCE among the group (36.7 – 39.1%). These values were within the historical value of the testing laboratory (0.06-0.36% for the frequency of MPCE and 20.4 – 52.3% for the PCE to NCE ratio).

Study Summary:

The clastogenicity of — was evaluated in a 4-week inhalation toxicity study in rats (Study U99-1565). The — degradation products were co-administrated with tiotropium by nose-only inhalation (15-min exposure/day) daily for four weeks. The concentrations of the degradants, expressed in relationship to tiotropium, were — Bone marrow samples (5/sex/treatment) were collected 24-30 hours after the last exposure. The frequency of MPCE was compared between the vehicle control (0.01% benzalkonium chloride and 0.05% EDTA), tiotropium (1.3 µg/kg/day) and tiotropium (1.4 µg/kg/day) spiked with the above degradants. The frequency of MPCE was similar between the vehicle control (0.23%) and tiotropium-treatment groups (0.24 – 0.25%). There was no significant difference in the ratio of PCE to NCE among the group (36.7 – 39.1%). These values were within the historical value of the testing laboratory (0.06-0.36%), so was the frequency of the PCE to NCE ratio. The validity of the study, however, is unknown.

9. Study title: Mutagenic Activity with — in the *Salmonella typhimurium* and *Escherichia coli* Assay

Key findings: No evidence of — mutagenicity was found.

Study no: U99-1650
Volume #, and page #: Vol. 56
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology, Birkendorfer Straβe 65, 88397 Biberach/Riss, Germany
Date of study initiation: 04-MAY-1999; end: 16-JUL-1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch II, , expiration on March 2000

Formulation/vehicle: DMSO

Methods:

Strains/species/cell line: S. typhimurium: TA 98, TA 100, TA 102, TA 1535, TA 1537; E. coli: WP2uvrA

Dose selection criteria:

Basis of dose selection: up to 5000 µg/plate. Precipitation occurred at 1,000 – 5000 µg/plate during plating and 5000 µg/plate after incubation.

Range finding studies: No.

Test agent stability: stable

Metabolic activation system: liver fractions from rats treated with Aroclor 1254

Controls:

Vehicle: water/ DMSO

Negative controls: the culture medium

Positive controls:

Non-activation: 2-nitrofluorene, sodium azide, mitomycin and 9-aminoacridine

Activation: 2-animoanthracene

Comments:

Exposure conditions:

Incubation and sampling times: Agar containing bacteria and the test material was incubated at 37°C for 48 and 72 hours.

Doses used in definitive study: 100, 300, 1,000, 3,000 and 5000 µg/plate

Study design: The ability of [redacted] to induce an increase in revertant colonies (result of point mutation) was evaluated in the Ames test in the absence and presence of the enzyme activation system. The study used five concentrations of [redacted], and the appropriate positive and negative controls.

Analysis: The number of revertant colonies.

Number of replicates: 3

Counting method: unspecified

Criteria for positive results: A reproducible, concentration dependent increase in the number of revertants of at least one tester strain over the vehicle control value and/or outside the historical control range.

Results:

Study validity: Valid.

Study outcome: No remarkable findings. The [redacted] treatment did not cause any apparent increase in the number of revertant colonies over the negative controls. The positive controls did produce marked increase in the number of revertant colonies.

Study Summary:

The mutagenicity of [redacted] was evaluated in the Ames test. *S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and *E. coli* WP2*uvr*A were treated with [redacted] at concentrations of 100-5,000 µg/plate in the presence and absence of the rat liver enzyme. The number of revertant colonies was counted and compared with the positive and negative controls. The positive control produced remarkable increases in the number of revertant colonies over the negative controls. The [redacted]-treated cells did not show any increase in the number of revertant colonies. [redacted] is considered non-mutagneic under the testing conditions.

10. Study title: Mutagenicity Study for Chromosomal Aberrations in Human *Lymhocytes in vitro* with —

Key findings: No evidence of — clastogenicity was found.

Study no: U99-1651
Volume #, and page #: Vol. 56
Conducting laboratory and location: Beohringer Ingelheim, Department of Experimental Pathology and Toxicology, Birkendorfer Straβe 65, 88397 Biberach/Riss, Germany
Date of study initiation: 15-MAR-1999; Ended on 16-AUG-1999
GLP compliance: yes
QA reports: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: Batch II, expiration date of March 2000

Formulation/vehicle: DMSO

Methods:

Strains/species/cell line: lymphocytes from blood of a healthy human volunteer.
Dose selection criteria:
Basis of dose selection: Solubility and cytotoxicity. — concentrations ranged from 3 to 5,000 µg/ml. Precipitation occurred at ≥ — in the first experiment and — in the second experiment. Cytotoxicity was defined as hemolysis (≥1,000 µg/ml) and decreases in mitotic index (≥ 1,000 µg/ml at 4-hour exposure and ≥ 600 µg/ml at 24-hour exposure).
Range finding studies: No.
Test agent stability: stable
Metabolic activation system: liver fractions from rats treated with Aroclor 1254
Controls:
Vehicle: water/ DMSO
Negative controls: the culture medium
Positive controls: cyclophosphamide and adriamycin
Comments:
Exposure conditions:
Incubation and sampling times: Lymphocyte cultures were treated with — for four hours (with or without activation) or 24 hours (without activation). The culture were harvested at 24 hours (regular harvest) or 48 hours (delayed harvest) from the start of the — treatment. Colcemid was added two hours before the harvest. The lymphocyte cultures were established by adding 0.25 ml whole blood from a healthy volunteer to 2.75 ml culture medium containing phytohaemagglutinin (a mitogen) and cultured for 48 hours prior to the treatment.
Doses used in definitive study: See Table 5.

Table 5. Study Design

Test	Duration of Treatment (hr)	Harvest Time (hr, post Treatment)		Concentrations (µg/ml)	
		Treatment	Analysis	Regular	Delayed
- S9 Exp. 1	4	20	-	3, 10, 30, 100, 200, 300, 600, 1000, 3000, 5000	100, 300, 1000
- S9 Exp. 2	24	0	24	Same as above	30, 100, 300
+ S9	4	20	-	300, 600, 1000	300

Analysis: Chromosomal aberrations and mitotic index.

Number of replicates: 2

Counting method: Unspecified. The mitotic index was evaluated from 1000 cells. Two hundred cells per concentration (100/culture) were evaluated for chromosomal aberration.

Criteria for positive results: A reproducible, concentration dependent increase in aberration frequency in the — treated cells ($p < 0.05$ in Fisher's Exact Test for multiple comparisons).

Results:

Study validity: Valid.

Study outcome: negative. The — treatment did not cause any increase in the frequency of chromosomal aberrations. The frequency of chromosomal aberrations were similar between the vehicle (1.0 – 1.5%) and the — treated samples (0 – 2.5%). These values were within the range of the historic control data (0 – 4.0%) of the testing laboratory. The positive controls did produce marked increase in the percentage of chromosomal aberrations (12.5 – 35.5%). The decrease in mitotic index was acceptable (by ≤ 50%) in the analyzed samples.

Study Summary:

The clastogenicity of — was evaluated an *in vitro* human lymphocyte chromosomal aberration assay. Cultured human lymphocytes from healthy volunteers were treated with — for four to 24 hours in the presence and absence of the rat liver enzymes. — concentrations were limited by the solubility (up to ' —). Chromosomal aberrations were analyzed and compared with the negative and positive controls. The frequency of chromosomal aberrations were similar between the vehicle (1.0 – 1.5%) and the — reated samples (0 – 2.5%). The positive controls did produce marked increase in the percentage of chromosomal aberrations (12.5 – 35.5%). — is considered non-clastogenic under the testing conditions.

III. GENERAL TOXICITY STUDIES

Two repeat-dose inhalation toxicity studies (Table 6) were conducted to evaluate the toxicity of — degradants of tiotropium. Acute IV or PO toxicity studies of the degradants were also conducted. These studies are not included in the table.

Table 6. General Toxicity Studies of Tiotropium Degradants

Study Description	Report #	Vol./p
— (aqueous solution) 13 week inhalation toxicity study in rats	U97-2187	54
4 week inhalation toxicity study of tiotropium bromide and degradation products — in rats	U00-1104	53

1. Study Title: Acute Oral and Intravenous Toxicity of — in Mice (Study U92-0584).

Mice (Chbb:NMRI, 5/sex/dose) were given by oral gavage one dose of 250 (female only), 350 (female only) 500, 700, 1,000 and 1,400 mg/kg; or by intraveonous injection, 8, 10 and 25 mg/kg of — . The mice were observed for 14 days before termination. Monitored parameters included clinical signs and necropsy. Mortality was used to determine LD_{50} using probit analysis. High doses caused mortality minutes after the drug administration. Table 6 presents the LD_{50} of —:

Table 6. LD_{50} (mg/kg) of — in Mice

	Route of Administration	
	Oral	Intravenous
Male	1,434	10.7
Female	1189	9.3

Findings included changes in clinical signs (prone or lateral position, ataxia, dyspnea, tremor and vocalization), in body weights (decrease), and necropsy (congestion in the liver, lungs, heart and kidneys in dead mice).

Dr. Satish Tripathi has reviewed the acute toxicity studies of other degradants previously (See review dated 26-AUG-1996).

2. Study title: Tiotropium Bromide (Ba 679 BR) and Accompanying Degradation Products

Repeat Dose Inhalation

Study in Rats over a period of 4 weeks

Key study findings: No remarkable toxicity associated with the degradants were revealed.

Study no:	U00-1104
Study type (if not reflected in title):	4-week inhalation toxicity study of the degradants in rats
Volume #, and page #:	vol. 53, p 1.
Conducting laboratory and location:	Boehringer Ingelheim Pharma KG, Germany: D-55216, Ingelhaim: in life, analysis of testing solutions, ... , D-88397 Biberach: Micronucleus analysis
Date of study initiation:	February 26, 1998
Date of Study Completion:	March 30, 1998
Study Report Date:	February 18, 2000
GLP compliance:	In compliance with OECD GLP
QA reports:	yes (x), no ( )
Drug, lot #, radiolabel, and % purity:	Batches, III and A

Ingredient	Content
Tiotropium Bromide	C
	a

* as percentage of tiotropium

Method (unique aspects):

Formulation/vehicle (Table 7):

Ingredient	Ba 679 BR Pure	Ba 679 BR plus Degradation Products	Vehicle
Ba 679 BR (0.05 %)	62 mg	62 mg	—
	—		—
	—		—
	—		—
	—		—

Dosing:

Species/strain: Wistar Rat [Chbb:THOM]

#/sex/group or time point (main study):	10/sex
Satellite groups used for toxicokinetics or recovery:	None
Age:	12 weeks at the start of the experiment
Weight:	Males: 307-403 g; females: 203-243 g
Doses in administered units:	
Route, form, volume, and infusion rate:	Nose-only Inhalation, aqueous aerosols, 15 min exposure/day (see Table 8)

Table 8. Design of Study U00-1104

Group	1	2	3
Animal #/sex	10	10	10
Tiotropium concentration:			
In the test solution (%)	0	0.05	0.05
In the test atmosphere (µg/L, intended)	0	2.2	2.2
MMAD (µm)		[redacted]	
Target dose (µg/kg)	0	20	20
Achieved total inhaled dose (µg/kg)[1]	0	18.7	19.8
Pulmonary deposited dose (µg/kg)[2]	0	1.31	1.38
Duration of Exposure (min)	15	15	15

1. Estimated as the following: Tiotropium (µg/kg) = (C x RMV x T)/BW, where: C = aerosol tiotropium concentration (µg/L), RMV = respiratory minute volume (ml/min) that is derived as 4.19 * (body weight)$^{0.66}$, T = duration of exposure (min), and BW = body weight (kg).
2. Derived as 7% of the total inhaled doses.
3. Tiotropium spiked with degradation products (see formulation for composition).

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Weeks 1 and 4
Blood pressure and heart rate:	Week 4 using sphygmogram on tail vain
Hematology:	Weeks 1 and 4
Clinical chemistry:	Weeks 1 and 4
Urinalysis:	Week 3
Gross pathology:	Terminal sacrifice
Organs weighed:	Adrenals; brain, heart, kidneys, liver, lungs, mandibular salivary glans, ovaries, pituitary, prostate, spleen, testes with epididymides, thymus thyroids and parathroid glands
Histopathology:	A complete panel
Toxicokinetics:	Not done
Other:	Aerosol particle diameter was determined on March 24 and 25, 1998

Results:

Mortality: None.

Clinical signs: The tiotropium-treated animals showed mydriasis. The respective total incidences of mydriasis was 147 and 153 in Group 2, and 114 and 121 in Group 3 for males and females.

Body weights: not remarkable.

Food consumption: The tiotropium-treated males showed a slight decrease in food consumption (Figure 1). Also there was no difference in body weights between the tiotropium and the spiked-tiotropium groups.

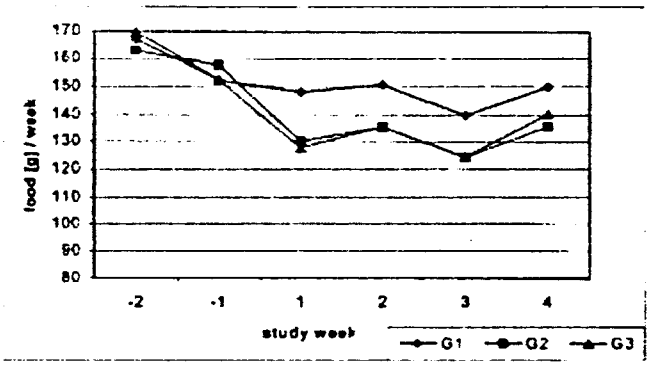

Figure 1. Food consumption-time course in male rats in Study U00-1104. G1 = control, G2 and G3 = tiotropium treatment at identical doses.

Ophthalmoscopy: The tiotropium-treated males showed binocular cataracts. The incidence of cataracts was 0/10, 2/10 and 4/10 for Groups 1, 2 and 3, respectively.

Cardiovascular system:

Blood pressure: no remarkable effects.

Heart rate: The tiotropium-treated rats showed increases in heart rates. The increase in mean heart rate was approximately 25% in the male and 11-18% in the female, respectively.

Hematology: no remarkable findings.

Clinical chemistry: no remarkable findings (Table 9).

Table 9. Clinical Chemistry Findings (Week 4)

Group	Male			Female		
	1 Control	2 Tiot. 1	3 Tiot. 2	1 Control	2 Tiot. 1	3 Tiot. 2
Total bilirubin (µmol/L)	2.3	2.62*	2.64*	2.1	2.65*	2.65*
Total cholesterol (mmol/L)	1.39	1.61*	1.61*	1.78	1.86	1.78

* Statistically significantly different from the control ($P < 0.05$).

Urinalysis: no remarkable findings

Organ weights: no remarkable findings.

Gross pathology: Tiotropium-treated rats showed deposits in the urinary bladder (male only), rectum stasis or dilation, and abnormality of the eye (Table 10)

Table 10. Gross Pathology Findings in Study U00-1104

Group	Male			Female		
	1	2	3	1	2	3
	Control	Tiot. 1	Tiot. 2	Control	Tiot. 1	Tiot. 2
N	10	10	10	10	10	10
Urinary deposition	0	7	3			
Lung discoloration/mis-shape	0	0	2			
Rectum stasis	0	3	3	0	0	2

a. One each for the following: fibrosis, hemorrhage, degeneration, demyelination, inflammation and atrophy.

Histopathology:

Table 11. Summary of Histopathology in Study U00-1104

Group	Male			Female		
	1	2	3	1	2	3
	Control	Tiot. 1	Tiot. 2	Control	Tiot. 1	Tiot. 2
N	10	10	10	10	10	10
Eye	3	1	1	0	6[a]	1
Urinary bladder deposition	0	6	0			
Larynx: debris	0	0	3			
Rectum dilation				1	0	3

Toxicokinetics: Not done.

Summary: This study evaluated the toxicity of tiotropium bromide and its — degradants. — Tiotropium doses were approximately 1.3 µg/kg/day. The respective doses of the degradants were — ng/kg/day for — and — ng/kg/day — Toxicity was evaluated by comparing animal's responses to the treatment of the vehicle, tiotropium, and tiotropium spiked with the degradants at the above concentrations. Both Groups 2 and 3 rats showed mydriasis, increases (11-25%) in the heart rate, rectum stasis (0/20-C, 3/10-G1 and 5/20-G2). The males also showed a decrease in body weight, deposits in the urinary bladder (0/10-C, 7/10-G1, and 3/10-G2), and debris in the larygnx (0/10-C, 0/10-G1 and 3/10-G2). The female showed a slight increase in the incidence of rectum dilation (1/10-C, 0/10-G1, 3/10-G2). The toxicity of G2 and G3 were similar.

3. Study title: [redacted] aqueous solution) 13-week inhalation toxicity study in rats

Key study findings:

Study no:	U97-2187
Study type (if not reflected in title):	13-week inhalation toxicity study of [redacted] an impurity and degradation product in rats
Volume #, and page #:	vol. 54
Conducting laboratory and location:	Boehringer Ingelheim Pharma KG, Germany: D-55216, Ingelhaim: in life, analysis of testing solutions, [redacted] and D-88397 Biberach: Micronucleus analysis
Date of study initiation:	March 14, 1994
Date of Study Completion:	July 26, 1994
Study Report Date:	August 15, 1997
GLP compliance:	In compliance with OECD GLP
QA reports:	yes (x), no ( )
Drug, lot #, radiolabel, and % purity:	Batch C, Expiration date: March 1995

Method (unique aspects):

Formulation/vehicle: 0.001, 0.05 and 2.0% aqueous solutions.

Dosing:

Species/strain:	Wistar/Chbb:THOM
#/sex/group or time point (main study):	10 (See Table 3)
Satellite groups used for toxicokinetics or recovery:	Toxicokinetics: 5/sex/group; Recovery: 10/sex each in the vehicle control and the high dose groups
Age:	10 – 11 weeks at the start of the experiment
Weight:	Males: 300 g; females: 218 g
Doses in administered units:	
Route, form, volume, and infusion rate:	Nose-only Inhalation, aqueous aerosols, 60 - 100 min exposure/day (see Table 12)

Table 12. Design of Study U98-2187

Group	1	2	3	4
Animal distribution				
Main Study	10	10	10	10
Recovery	10	-	-	10
Toxicokinetics	5	5	5	5
Duration of Exposure	100	60	60	100
$MMAD_{wk\ 14}$ (µm)				
Aerosol — conc. (µg/l)	-	0.027	0.184	7.32
Dose Estimates				
Target dose (µg/kg)	-	2	100	4000
Achieved total inhaled dose (µg/kg)[1]	-	1.3	76.6	3024
Pulmonary deposited dose (µg/kg)[2]	-	0.1	5.4	212
Duration of Exposure (min)	15	15	15	15

1. Estimated with a minute volume of 182, 178 and 173 ml/min for low, mid and high dose groups (both males and females), respectively. See Study U00-1104 for more details in estimation of the achieved total inhaled dose.
2. Derived as 7% of the total inhaled doses.

Observations and times:

Clinical signs: Daily
Body weights: Weekly
Food consumption: Weekly
Ophthalmoscopy: Weeks 6, 10, 13 (main study), 14 and 18 (recovery)
Blood pressure and heart rate: Weeks –1, 5 and 12 using sphygmogram on tail vain
Hematology: Weeks 1, 4 and 13
Clinical chemistry: Weeks 1, 4 and 13
Urinalysis: Weeks 1, 4, 13 and 19 (recvery)
Gross pathology: Terminal sacrifice
Organs weighed: Adrenals; brain, heart, kidneys, liver, lungs, mandibular salivary glans, ovaries, pituitary, prostate, spleen, testes with epididymides, thymus thyroids and parathroid glands
Histopathology: A complete panel for the control and high dose groups; selected tissues in the mid and low dose group.
Toxicokinetics: Days 10 and 86
Other: Aerosol particle sizes: Weeks 2 and 13

Results:

Mortality: No treatment-related mortality was observed. Four male rats (1-MD and 3-HD/recovery) died during or soon after the blood sampling for clinical pathology testing. The deaths were not considered treatment-related because the rats died during blood sampling procedure. The time of death was weeks 4 and 13 (HD) and 14 (MD). Pathology evaluation indicated that these rats died of acute cardiorespiratory failure.

Clinical signs: The mid and high dose rats showed severe mydriasis. The mydriasis is transient in the mid dose group but permanent in the high dose group. The mydriasis disappeared one week after the secession of the treatment.

Body Weights (Table 13):

Table 13. Body Weight (g) in Study U97-2187

	Male				Female			
	0	LD	MD	HD	0	LD	MD	HD
Pre-treatment	298	298	302	301	218	218	216	219
Week 1	305	305	304	292*	215	217	215	213
Week 6	371	361	349	328*	248	248	238	233*
Week 13	417	406	388*	356*	259	262	246	237*
Week 19	458	-	-	406	278	-	-	274

* $p < 0.05$.

Body length: The report indicated that the dose-proportional decrease in body length was also observed, but did not contain data to support the observation.

Food consumption: The tiotropium-treated males showed a slight decrease in food consumption (Table 14).

Table 14. Feed Consumption (g) in Study U97-2187

	Male				Female			
	0	LD	MD	HD	0	LD	MD	HD
Pre-treatment	150	152	152	153	108	111	113	110
Week 1	128	139	119	99*	87	91	84	70*
Week 6	146	141	133*	130*	107	110	103	98*
Week 13	131	130	124	113*	101	99	96	87*
Week 19	133	-	-	130	102	-	-	98

* $p < 0.05$.

Ophthalmoscopy (Table 15):

Table 15. Ophthalmoscopic Findings in Study U97-2187 (high dose only)

Time	Week 6	Week 13	Week 14	Week 18
Male	3/10	8/10	4/8	4/8
Female	1/10	4/10	6/9	4/9

Cardiovascular system:

Blood pressure: no remarkable effects.

Heart rate (Table 16):

Table 16. Heart Rate (bpm) in Study U97-2187 (means of male and females, n = 20)

—	0	LD	MD	HD
Pre-treatment	466	427	488	457
Week 5	434	403	509*	502*
Week 12	423	410	505*	505*

* $p < 0.05$.

Hematology: no remarkable findings.
Clinical chemistry: no remarkable findings.
Urinalysis: no remarkable findings.
Body length: see Table 17.

Table 17. Body Length (mm) in Study U97-2187 (n = 20)

Sex	Vehicle Control	— High Dose
Male (main)	255.9	245.1*
(recovery)	265.2	257.0*
Female	223.6	216.1*

* $p < 0.05$.

Organ weights: no remarkable findings.
Gross pathology: no remarkable findings.

Histopathology (Table 18): The high dose rats also showed the extension and/or venous congestion of the gastrointestinal tract, venous congestion of urinary bladder, pituitary glands and kidney, lymph node erythorophagocytosis, thymus cysts, pancreas cell vacuolation and decryoadenitis of the Harderian glands. The pancreas cell vacuolation, venous congestion of pituitary glands and kidney, pancreas cysts and decryoadenitis of the Harderian glands were also apparent in the recovery rats.

Toxicokinetics: The following plasma drug levels were detected: below the limit of quantitation - low dose, — ng/ml – mid dose, and — ng/ml – high dose. The highest concentration were seen 10 minutes after inhalation.

Summary: Wistar rats (10/sex/group) were given via nose-only inhalation the vehicle, 0.01, 5.4, or 212 µg/kg/day of — for 13 weeks. Additional rats (10 rats/sex) were included in the vehicle and high dose groups to study reversibility of lesions after a recovery period of 4 weeks. Histology examinations were conducted in the vehicle control and high dose groups, and selected tissues in the mid dose group. The mid and high dose rats showed mydriasis and decreases in body weights (5-7% for mid dose and 9 – 15% for high dose, respectively). The high dose rats also showed decreases in body length (approximately 3.5%) and feed consumption, the extension and/or venous congestion of the gastrointestinal tract, venous congestion of urinary bladder, pituitary glands and kidney, lymph node erythorophagocytosis, thymus cysts, pancreas cell vacuolation and decryoadenitis of the Harderian glands. The

pancreas cell vacuolation, venous congestion of pituitary glands and kidney, pancreas cysts and decryoadenitis of the Harderian glands were also apparent in the recovery rats.

This study failed to establish a NOAEL value because histological evaluation of low and mid groups was incomplete.

Table 18. Histopathlogy Findings in Study U97-2187

Group	Male				Female			
	1	2	3	4	1	2	3	4
	0	LD	MD	HD	0	LD	MD	HD
N	10	10	10	10	10	10	10	10
Salivary glands/enlarged	0	0	9	10	0	0	10	10
Stomach/extended glands	5	-	-	10	4	-	-	4
Cecum/venous congestion	2	-	-	6	1	-	-	5
Rectum/venous congestion	2	-	-	4	3	-	-	5
Pancreas/ vacuolated cell	4	-	-	8	6	-	-	8
vacuolated cell (rec.)	1	-	-	5	5	-	-	6
Kidney/venous congestion (VC)	3	-	-	7	3	-	-	5
/VC (recovery group)	1	-	-	2	0	-	-	2
U. Bladder/ VC	3	-	3/8	6	4	-	-	4
/ VC	1	-	-	2	1	-	-	6
Pituitary Gland/ VC	2	-	0/1	1	3	-	-	6
/ VC (recovery)	7	-	-	7	7	-	-	7
Lymph node/cervical/ crythrophagosytosis	1	-	-	3	1	-	-	3
Thymus/ cysts	1	-	-	4	2	-	-	8
/ cysts (recovery)	2	-	-	4	2	-	-	3
Eye/ granular tissue	1	-	-	7	2	-	-	2
/ granular tissue	4	-	-	3	0	-	-	1
Harderian gland/ decryoadenitis	3	-	-	5	2	-	-	7
HG/ decryoadenitis (receovery)	2	-	-	5	4	-	-	10

IV. OVERALL SUMMARY AND CONCLUSION

A. Summary

General and genetic toxicity studies were conducted to qualify the tiotropium impurities. The studies included 10 genetic toxicity tests, several acute toxicity studies, and two repeat-dose inhalation toxicity studies up to 13 weeks in treatment. The genetic studies were the bacterial gene mutation assay, the micronucleus assays in mice and rats, the human lymphocyte chromosomal aberration assay and the UDS assay in rat hepatocytes. Two to three assays were completed for each degradant. None of degradants tested positive under the assay conditions. The repeat dose toxicity studies

were a 13-weeks inhalation toxicity study of [redacted] and a 4-week inhalation toxicity study of tiotropium spiked with [redacted] impurities. The repeat-dose toxicity studies, although not comprehensive, showed that the toxicity profile of tiotropium spiked with impurities were similar to that of tiotropium.

B. Evaluation

Tiotropium degrades in storage. The levels of the degradants increase as a function of time. Table 1 (page 2) shows the proposed release and shelf-life specifications for the degradants of safety concern. These degradants ([redacted] , are of safety concern because their levels are above the ICH qualification threshold levels: not-more-than 0.1% in the drug substance and 1.0% in drug product, respectively. [redacted] , is present in the drug substance and the remaining degradants (up to [redacted] each) are represent in the drug product. Figure 1 presents the degradation pathways for tiotropium (code named BA 679 BR) and structures of its degradants.

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Figure 2. Degradation pathways for tiotropium

As indicated in the summary section, the sponsor has conducted studies to evaluate the safe of the degradants. Table 19 presents the testing scheme of the impurities. These studies reveal no specific signal of safety concerns regarding to the proposed levels of the degradants; however, they are insufficient to support the safety of the proposed degradant levels. The reasons are:

1) The inadequate treatment duration of their repeat-dose inhalation toxicity studies:
   a. 4 weeks for [redacted] , and
   b. None for [redacted]
2) The failure to establish a NOAEL for [redacted]

Thus, the toxicological characterization of the degradants is incomplete. The current Division policy requires a treatment-duration of 13 weeks to qualify impurities. General toxicity data supporting the proposed specification is a 4-week toxicity study of tiotropium spiked with several impurities. A test-duration of 4 weeks or less is considerably shorter than 13 weeks required for drugs indicated for asthma by the Division. In addition, The level of [redacted], was only one-fifth of the level (up to [redacted], in the drug product although the level of other degradants was generally the same as the proposed. Furthermore, [redacted] nas not been studied in any repeat dose toxicity studies. Finally, the 13-week inhalation study of [redacted] failed to establish a NOAEL for the compound. A NOAEL is needed for the determination of an acceptable level of [redacted] especially when the 13-weeks NOAEL data indicate that [redacted] might be more potent than tiotropium (5 µg/kg/day). In short, the application has not fulfilled the requirement of adequately testing the compounds of interest for 13 weeks.

Table 19. Overview of Preclinical Safety Evaluation of Tiotropium Degradants

Degradants	[redacted]					
Levels present in						
Drug Substance (%)						
Drug product						
Genetic toxicology[c]						
Gene Mutation *In vitro*	✓	✓	✓	✓	✓	✓
Chrom. Ab. *in vitro*					✓	
Chrom. Ab. *in vivo*	✓	✓	✓	✓		✓
Chrom. Ab. Human lymph.						
UDS		✓				
Inhalation toxicology						
Acute toxicity (IV or PO)	✓	✓	✓	✓		✓
4-week study[d]	✓		✓	✓		✓
13-week study		✓				

a. As [redacted]
b. As [redacted] The sum may not exceed [redacted]
c. No evidence of genotoxicity was found in the checked assays.
d. The level of the degradants in the testing material was the same as the proposed specifications in the to-be-marketed product.

The sponsor of the application argues that the degradants have been qualified for the following three reasons:

1. The degradants have very week, or no cholinergic activity based on their affinity to the five muscarinic receptor subtypes.
2. The degradant are [redacted] n the plasma.
3. Degradants [redacted] have been tested concomitantly with tiotropium in "numerous repeat-dose toxicity studies ... including the carcinogenicity assays.

These arguments are inadequate. The first argument does not exclude the possibility that the degradants may act through a [redacted] mechanism. Although the affinity of the degradants [redacted] to muscarinic receptors is 10,000 – 100,000 fold lower than that of tiotropium (Study 93-0507), systemic toxicity of these compounds are rather similar (Table 20). Tiotropium has a LD50 of 21 mg/kg. [redacted] and [redacted] have LD50 of 10 and 16 mg/kg, respectively. The remarkable differences in the cholinergic receptor affinity and the striking similarity in the LD50s between tiotropium and its degradants suggest that these degradants could act through mechanism(s) of non-muscarinic cholinergic receptor activation.

Table 20. Median Lethal Dose (LD_{50}) of Tiotropium Degradants in Mice

Route of Administration	Approximate LD50 (mg/kg)[1]					
	[redacted]					Tiotro-pium
Intravenous	154.7	10	> 200[1]	> 16	148	20.6
Oral		1,200				4,000

1. Source: Table 3.6.6.3.1.1 (vol 1, p 106) of the submission.

The level of the degradants in the non-clinical testing material is too low to support the sponsor's second argument. According to the submission of July 25, 2002 that summarizes the level of impurities in eight batches of tiotropium used in non-clinical studies[2], the degradant levels in the toxicology program are:

[redacted] < [redacted]
[redacted] < [redacted]
[redacted] < [redacted] for 7 batches (exception: [redacted] for Batch I).
[redacted] < [redacted]
[redacted] < [redacted] for repeat dose studies and [redacted] (Batch IV) for an acute IV toxicity in rats and an acute inhalation toxicity study in dogs

Clearly, the degradant levels in the toxicity studies ([redacted] is far below their proposed level in the to-be-marketed product ([redacted] Such levels do not qualify the proposed specification. Neither is the estimated daily exposure on a mg/kg basis. Study U91-0493 is a 13-week inhalation toxicity study in rats. It has the highest reported level of [redacted] of [redacted] and a tiotropium NOAEL value of approximately ≤ 5 µg/kg/day. Consequently, the estimated pulmonary exposure of [redacted] is [redacted] ng/kg/day, a level that is lower than its estimated daily exposure [redacted] g/kg/day in humans. The human exposure is based on an impurity level of [redacted] and a maximum recommended daily dose of 18 µg/kg for a patient of 50 kilograms. Apparently, no safety margin exists. Thus, the impurity level in the toxicology program does not qualify their proposed specifications.

[2] The submission was a correspondence to the Division's March 14, 2002 information request.

Overall, the sponsor has not provided sufficient preclinical data to support the safety of the proposed specifications for these degradants and impurities: — — in the drug product, and — in the drug substance.

3. Recommendation

The proposed level of the degradant in tiotropium product is not acceptable. The sponsor should:

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

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

/S/

Luqi Pei, Ph.D.
Pharmacologist and Toxicologist

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
8/28/02 02:14:38 PM
PHARMACOLOGIST

Joseph Sun
8/28/02 04:36:46 PM
PHARMACOLOGIST
I concur.

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21395/000	Action Goal:	
Submitted:	13-DEC-2001	District Goal:	14-AUG-2002
Regulatory Due:	01-FEB-2004	Brand Name:	SPIRIVA (TIOTROPIUM
Applicant:	BOEHRINGER INGELHEIM	Estab. Name:	BROMIDE) POWDER
	OLD RIDGEBURY RD	Generic Name:	TIOTROPIUM BROMIDE
	DANBURY, CT 06811		
Priority:	1S	Dosage Form:	(AEROSOL)
Org Code:	570	Strength:	18 MCG/INHALATION

Application Comment:

FDA Contacts:	A. ZECCOLA	(HFD-570)	301-827-1058	, Project Manager
	B. ROGERS	(HFD-570)	301-827-1065	, Review Chemist
	G. POOCHIKIAN	(HFD-800)	301-827-5918	, Team Leader

Overall Recommendation: ACCEPTABLE on 29-AUG-2003by S. FERGUSON(HFD-322)301-827-9009

ACCEPTABLE on 03-DEC-2002by J. D AMBROGIO(HFD-322)301-827-9049

ACCEPTABLE on 29-NOV-2002by S. ADAMS (HFD-322)301-827-9051

Establishment: CFN 9610492 FEI 3002806556

BOEHRINGER INGELHEIM KG

INGELHEIM AM RHEIN, , GM

DMF No: AADA:

Responsibilities:

- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE PACKAGER
- DRUG SUBSTANCE RELEASE TESTER
- DRUG SUBSTANCE STABILITY TESTER
- FINISHED DOSAGE MANUFACTURER

Type: ADM OAI Status: NONE

Estab. Comment: SITE ADDRESS IN APPLICATION IS BOEHRINGER INGELHEIM PHARMA KG, BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, GERMANY. SITE IS REPONSIBLE FOR

TIOTROPIOM INHALATION POWDER, HARD CAPSULES 18 MCG. (OR 27-FEB-2002 by

B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	PS			DAMBROGIOJ
INSPECTION SCHEDULED	21-AUG-2002		16-SEP-2002		IRIVERA
INSPECTION PERFORMED	16-SEP-2002		16-SEP-2002		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
INSPECTION PERFORMED	16-SEP-2002		16-SEP-2002		DAMBROGIOJ
See completed report.					
DO RECOMMENDATION	24-OCT-2002			ACCEPTABLE	ADAMSS

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

		INSPECTION	
AWAITING EIR			
OC RECOMMENDATION	24-OCT-2002	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	
OC RECOMMENDATION	18-NOV-2002	ACCEPTABLE	ADAMSS
		DUPLICATE MILESTONE FROM FACTS	
SUBMITTED TO OC	26-AUG-2003		ROGERSB
OC RECOMMENDATION	26-AUG-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	

Profile: CSN OAI Status: NONE

Est. Comment: ADDRESS OF SITE IN APPLICATION IS BOEHRINGER INGELHEIM PHARMA KG, BINGER STRASSE 173, 55216 INGELHEIM AM RHEIN, GERMANY. SITE IS RESPONSIBLE FOR ALL ASPECTS OF THE MANUFACTURING, PACKAGING, LABELING, AND CONTROL OPERATIONS (INCLUDING POST-APPROVAL STABILITY TESTING) IN THE PRODUCTION OF TIOTROPIUM BROMIDE MONOHYDRATE DRUG SUBSTANCE. (on 27-FEB-2002 by B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	PS			DAMBROGIOJ
INSPECTION SCHEDULED	21-AUG-2002		16-SEP-2002		IRIVERA
INSPECTION PERFORMED	16-SEP-2002		16-SEP-2002		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
INSPECTION PERFORMED	16-SEP-2002		16-SEP-2002		DAMBROGIOJ
See completed report.					
OC RECOMMENDATION	21-OCT-2002			ACCEPTABLE	FERGUSONS
				DISTRICT RECOMMENDATION	

DUPLICATE MILESTONE FROM FACTS

SUBMITTED TO OC	26-AUG-2003		ROGERSB
OC RECOMMENDATION	26-AUG-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON PROFILE	

Establishment: CFN 9610551 FEI 3002806518

BOEHRINGER INGELHEIM PHARMA KG

BIBERACH AN DER RISS, , GM

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

APPEARS THIS WAY ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Estab. Comment: SITE ADDRESS IN APPLICATION IS BOEHRINGER INGELHEIM PHARMA KG, BIRKENDORFERSTR. 65, D-88397 BIBERACH/RISS, GERMANY. SITE IS RESPONSIBLE FOR TESTING

(on 28-FEB-2002 by B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	21-AUG-2002		19-SEP-2002		IRIVERA
INSPECTION PERFORMED	18-SEP-2002		18-SEP-2002		DAMBROGIOJ
AUTOMATIC WITHHOLD STATUS ISSUED BY FACTS, See attached report					
INSPECTION PERFORMED	19-SEP-2002		19-SEP-2002		ADAMSS
CTION SCHEDULED	28-SEP-2002		20-OCT-2002		DAMBROGIOJ
DO RECOMMENDATION	24-OCT-2002			ACCEPTABLE INSPECTION	ADAMSS
NO 483. AWAITING EIR					
OC RECOMMENDATION	24-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
OC RECOMMENDATION	18-NOV-2002			ACCEPTABLE DUPLICATE MILESTONE FROM FACTS	ADAMSS
OC RECOMMENDATION	02-DEC-2002			ACCEPTABLE DUPLICATE MILESTONE FROM FACTS	ADAMSS
SUBMITTED TO OC	26-AUG-2003				ROGERSB
OC RECOMMENDATION	26-AUG-2003			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

Establishment: CFN FEI 1000110912

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

Estab. Comment: SITE ADDRESS IN APPLICATION IS [redacted] ALTERNATE SITE FOR [redacted] OF HANDIHALER DEVICE PORTION OF DRUG PRODUCT.

(on 28-FEB-2002 by B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
OC RECOMMENDATION	12-MAR-2002			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ
SUBMITTED TO OC	26-AUG-2003				ROGERSB
OC RECOMMENDATION	26-AUG-2003			ACCEPTABLE	DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

BASED ON PROFILE

Establishment: CFN FEI

[redacted]

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

P le: CSS OAI Status: NONE

Estab. Comment: SITE ADDRESS IN APPLICATION IS [redacted] SITE IS RESPONSIBLE FOR [redacted] (on 11-MAR-2002 by B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	PS			DAMBROGIOJ
INSPECTION SCHEDULED	21-AUG-2002		18-OCT-2002		IRIVERA
INSPECTION PERFORMED	17-OCT-2002		17-OCT-2002		MLOPEZ
DO RECOMMENDATION	24-OCT-2002			ACCEPTABLE INSPECTION	ADAMSS
AWAITING EIR					
COMMENDATION	24-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-AUG-2003				ROGERSB
OC RECOMMENDATION	26-AUG-2003			ACCEPTABLE	DAMBROGIOJ

Establishment: CFN PEI

DMF No: AADA:

Responsibilities:

Profile: CTL OAI Status: NONE

Estab. Comment:

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

ADDRESS IN APPLICATION IS [redacted]

[redacted] SITE IS

RESPONSIBLE FOR [redacted]

[redacted] (on 11-MAR-2002 by B. ROGERS (HFD-570) 301-827-1063)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	21-AUG-2002		06-SEP-2002		IRIVERA
INSPECTION PERFORMED	11-OCT-2002		11-OCT-2002		IRIVERA
NO FD-483 WAS ISSUED, FIRM IS ACCEPTABLE.					
DO RECOMMENDATION	29-NOV-2002			ACCEPTABLE INSPECTION	ADAMSS
OC RECOMMENDATION	29-NOV-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-AUG-2003				ROGERSB
OC RECOMMENDATION	26-AUG-2003			ACCEPTABLE BASED ON FILE REVIEW	DAMBROGIOJ

Establishment: FEI

[redacted]

DMF No: AADA:

Responsibilities: FINISHED DOSAGE OTHER TESTER

P: :: CTL OAI Status: NONE

Estab. Comment: SITE ADDRESS IN APPLICATION IS [redacted]

[redacted] (on 28-FEB-2002 by B. ROGERS (HFD-570) 301-827-1065)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
[illegible]MITTED TO OC	11-MAR-2002				ROGERSB
SUBMITTED TO DO	12-MAR-2002	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	12-MAR-2002	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	28-SEP-2002		22-OCT-2002		IRIVERA
INSPECTION PERFORMED	22-OCT-2002		22-OCT-2002		MLOPEZ
DO RECOMMENDATION	24-OCT-2002			ACCEPTABLE INSPECTION	ADAMSS
NO 483 ISSUED. AWAITING EIR FROM INVESTIGATOR.					
OC RECOMMENDATION	24-OCT-2002			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
SUBMITTED TO OC	26-AUG-2003				ROGERSB

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

OC RECOMMENDATION	26-AUG-2003	ACCEPTABLE	DAMBROGIOJ
		BASED ON FILE REVIEW	

AC EI 10/22/02.

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21395/000
Org Code : 570
Priority : 1S

Sponsor: BOEHRINGER INGELHEIM
OLD RIDGEBURY RD
DANBURY, CT 06811

Stamp Date : 13-DEC-2001
PDUFA Date : 13-OCT-2002
Action Goal :
District Goal: 14-AUG-2002

Brand Name : SPIRIVA (TIOTROPIUM BROMIDE) POWDER
Estab. Name:
Generic Name: TIOTROPIUM BROMIDE
Dosage Form: (AEROSOL)
Strength : 18 MCG/INHALATION

FDA Contacts:			
A. ZECCOLA	Project Manager	(HFD-570)	301-827-1058
B. ROGERS	Review Chemist	(HFD-570)	301-827-1065
G. POOCHIKIAN	Team Leader	(HFD-570)	301-827-1050

Overall Recommendation: ACCEPTABLE on 03-DEC-2002by J. D AMBROGIO(HFD-324) 301-827-0062
ACCEPTABLE on 29-NOV-2002by S. ADAMS (HFD-324) 301-594-0095

Establishment : CFN : 9610492 FEI : 3002806556
BOEHRINGER INGELHEIM KG
INGELHEIM AM RHEIN, , GM
DMF No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

Profile : ADM OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-02
Decision : ACCEPTABLE
Reason : DUPLICATE MILESTONE FROM FACTS
Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 18-NOV-02
Decision : ACCEPTABLE
Reason : DUPLICATE MILESTONE FROM FACTS

Establishment : CFN : 9610551 FEI : 3002806518
BOEHRINGER INGELHEIM PHARMA KG
BIBERACH AN DER RISS, , GM
DMF No: AADA:

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-DEC-02
Decision : ACCEPTABLE
Reason : DUPLICATE MILESTONE FROM FACTS

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CSS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-NOV-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 24-OCT-02
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI : 1000110912

DMF No: AADA:

Responsibilities:

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile :	CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-MAR-02		
Decision :	ACCEPTABLE		
Reason :	BASED ON PROFILE		

2 Page(s) Withheld

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21395/000
Org Code : 570
Priority : 1S

Sponsor: BOEHRINGER INGELHEIM
OLD RIDGEBURY RD
DANBURY, CT 06811

Stamp Date : 13-DEC-2001
PDUFA Date : 13-OCT-2002
Action Goal :
District Goal: 14-AUG-2002

Brand Name : SPIRIVA (TIOTROPIUM BROMIDE) POWDER
Estab. Name:
Generic Name: TIOTROPIUM BROMIDE
Dosage Form: (AEROSOL)
Strength : 18 MCG/INHALATION

FDA Contacts:			
A. ZECCOLA	Project Manager	(HFD-570)	301-827-1058
B. ROGERS	Review Chemist	(HFD-570)	301-827-1065
G. POOCHIKIAN	Team Leader	(HFD-570)	301-827-1050

--Overall Recommendation:

Establishment : CFN : 9610492 FEI : 3002806556
BOEHRINGER INGELHEIM KG
INGELHEIM AM RHEIN, , GM
DMF No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

Profile : ADM OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 28-SEP-02

Profile : CSN OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 17-SEP-02

Establishment : CFN : 9610551 FEI : 3002806518
BOEHRINGER INGELHEIM PHARMA KG
BIBERACH AN DER RISS, , GM
DMF No: AADA:

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 28-SEP-02

Establishment : CFN : FEI :

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CSS OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 21-AUG-02

Establishment : CFN : FEI :

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 21-AUG-02

Establishment : CFN : FEI :

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 28-SEP-02

Establishment : CFN : [redacted] FEI : 1000110912

[redacted]

DMF No: AADA:

Responsibilities: [redacted]

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile	: CTL	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	12-MAR-02		
Decision	: ACCEPTABLE		
Reason	: BASED ON PROFILE		

APPEARS THIS WAY
ON ORIGINAL

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application : NDA 21395/000
Org Code : 570
Priority : 1S

Sponsor: BOEHRINGER INGELHEIM
OLD RIDGEBURY RD
DANBURY, CT 06811

Stamp Date : 13-DEC-2001
PDUFA Date : 13-OCT-2002
Action Goal :
District Goal: 14-AUG-2002

Brand Name : SPIRIVA (TIOTROPIUM BROMIDE) POWDER
Estab. Name:
Generic Name: TIOTROPIUM BROMIDE
Dosage Form: (AEROSOL)
Strength : 18 MCG/INHALATION

FDA Contacts:			
A. ZECCOLA	Project Manager	(HFD-570)	301-827-1058
B. ROGERS	Review Chemist	(HFD-570)	301-827-1065
G. POOCHIKIAN	Team Leader	(HFD-570)	301-827-1050

--Overall Recommendation:

Establishment : CFN : 9610492 FEI : 3002806556
BOEHRINGER INGELHEIM KG
INGELHEIM AM RHEIN, , GM
DMF No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
FINISHED DOSAGE MANUFACTURER

Profile : ADM OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 17-SEP-02

Profile : CSN OAI Status: NONE
Last Milestone: INSPECTION PERFORMED
Milestone Date: 17-SEP-02

Establishment : CFN : 9610551 FEI : 3002806518
BOEHRINGER INGELHEIM PHARMA KG
BIBERACH AN DER RISS, , GM
DMF No: AADA:

Responsibilities:
FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 21-AUG-02

Establishment : CFN : FEI :

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

DMF No: AADA:

Responsibilities:

Profile : CSS OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 21-AUG-02

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: INSPECTION SCHEDULED
Milestone Date: 21-AUG-02

Establishment : CFN : FEI :

DMF No: AADA:

Responsibilities:

Profile : CTL OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 12-MAR-02

Establishment : CFN : FEI : 1000110912

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 12-MAR-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : FEI :

[redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : ADM OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 12-MAR-02
:
:
