CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076644Orig1s000

Name: Oxybutynin Chloride Extended-release Tablets
10 mg

Sponsor: Mylan Pharmaceuticals, Inc.

Approval Date: November 9, 2006

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

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Microbiology Review(s)	
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

APPROVAL LETTER

ANDA 76-644

NOV 9 2006

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
Vice President, Regulatory Affairs
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 21, 2003, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Oxybutynin Chloride Extended-release Tablets, 10 mg.

Reference is made to the Tentative Approval letter issued by this office on January 12, 2005, and to your amendments dated February 18, June 9, and July 27 (two amendments), 2004; and August 19, September 16, September 21, and October 27, 2005. We also acknowledge receipt of your correspondence dated July 19, August 31, September 16, and September 29, 2005, and August 17, 2006, regarding the '092 patent as noted below and informing the agency of the outcome of your patent litigation regarding the '355 patent.

We have completed the review of this ANDA as amended, and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the ANDA is approved. The Division of Bioequivalence has determined your Oxybutynin Chloride Extended-release Tablets, 10 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug, Ditropan XL Extended-release Tablets, 10 mg, of Alza Corporation. Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application. The "interim" dissolution specifications are as follows:

Time	Percent Dissolved
2 hr:	0 - 10%
4 hr:	10 - 30%
8 hr:	40 - 65%
16 hr:	NLT 80%

The "interim" dissolution test(s) and tolerances should be finalized by submitting dissolution data from the first three production size batches. These data should be submitted as a "Special Supplement - Changes Being Effected" if there are no revisions to be made to the "interim" specifications or when the final specifications are tighter than the "interim" specifications. In all other instances, the information should be submitted in the form of a Prior Approval Supplement.

The listed drug product referenced in your ANDA, Ditropan XL Extended-release Tablets, 10 mg, of Alza Corporation, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date*
5,674,895 (the '895 patent)	November 22, 2015
5,840,754 (the '754 patent)	November 22, 2015
5,912,268 (the '268 patent)	November 22, 2015
6,124,355 (the '355 patent)	November 22, 2015
6,262,115 (the '115 patent)	November 22, 2015
6,919,092 (the '092 patent)	November 22, 2015

*with pediatric exclusivity

Your ANDA contains paragraph IV patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents is invalid, unenforceable, or will not be infringed by your manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-release Tablets, 10 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action was brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of one or more of the patents that were the subjects of the paragraph IV certifications. This action must have been brought against

Mylan prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act. As a result, litigation for infringement of the '355 patent was brought against Mylan in the United States District Court for the Northern District of West Virginia (Alza Corporation v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 1:03-cv-158). Following receipt of the tentative approval letter, you informed the agency that Mylan prevailed in the district court with respect to the finding that Mylan did not infringe the asserted claims of the '355 patent. Therefore, under section 505(j)(5)(B)(iii)(I), this court decision renders the ANDA eligible for approval. Furthermore, you informed the agency that on October 11, 2005, Alza appealed the district court decision, and that on September 6, 2006, the U.S. Court of Appeals for the Federal Circuit affirmed the district court's holding that Mylan's product does not infringe the asserted claims of the patent and that the asserted claims are invalid.

The agency recognizes that Mylan was not sued within the 45-day period on any of the other listed patents.

With respect to 180-day generic drug exclusivity, we note that Mylan was the first ANDA applicant to submit a substantially complete ANDA with a paragraph IV certification for Oxybutynin Chloride Extended-release Tablets, 10 mg, to each of the listed patents. Therefore, with this approval, Mylan is eligible for 180-days of market exclusivity for Oxybutynin Chloride Extended-release Tablets, 10 mg. This exclusivity, which is provided for under section 505(j)(5)(8)(iv) of the Act,[1] will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv). Please submit correspondence to the ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

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[1] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

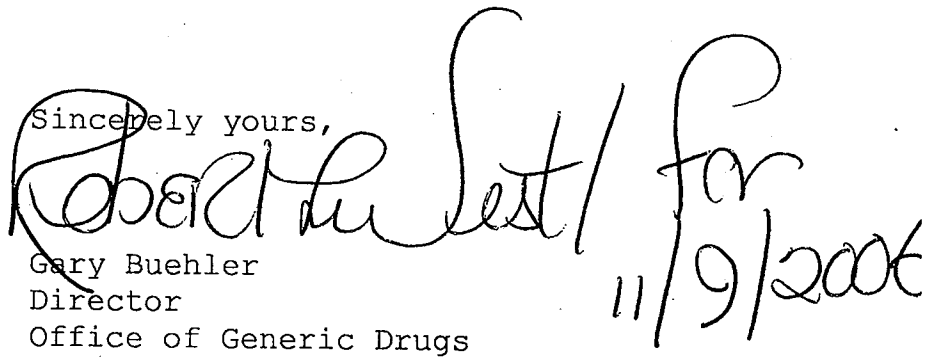
Post-marketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-644
Division File
Field Copy
HFD-610/R. West
HFD-600/C. Parise
HFD-604/D. Hare
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-630/M.Darj/ Mitch DARJ 21 NOV 05
HFD-630/D.Gill/ DSGill 11-21-05
HFD-617/S.Park/ SPark 11/23/05
HFD-613/P.Birch/
HFD-613/J.Grace/

Approved Electronic Labeling Located at:
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL1.pdf
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL2.pdf
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed OT.pdf

V:\FIRMSAM\MYLAN\LTRS&REV\76644.ap.doc

F/T by:

APPROVAL

CMC no change satisfactory. Margaret Sayre 2/14/06

Robert West 8/16/2006 pending CR response.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76644Orig1s000

TENTATIVE APPROVAL LETTER

ANDA 76-644

JAN 12 2005

Mylan Pharmaceuticals Inc.
Attention: S. Wayne Talton
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated January 21, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Oxybutynin Chloride Extended-release Tablets, 10 mg.

Reference is also made to your amendments dated December 2, 2003; and July 27, August 20, September 24, and October 13, 2004. We also acknowledge receipt of your correspondence dated May 27, and July 22, 2003, addressing the patent issues noted below.

We have completed the review of this abbreviated application, and based upon the information you have presented to date we have concluded that the drug is safe and effective for use as recommended in the submitted labeling. However, we are unable to grant final approval to your application at this time because of the patent issue noted below. Therefore, the application is **tentatively approved**. This determination is based upon information available to the agency at this time (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). This determination is subject to change on the basis of new information that may come to our attention. In addition, this letter does not address notice issues related to the 180-day exclusivity provisions under Section 505(j)(5)(B)(iv) of the Act.

The listed drug product referenced in your application, Ditropan XL Extended-release Tablets, 10 mg, of Alza Corporation, is subject to periods of patent protection. The

following patents and their expiration dates are currently listed in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book":

U.S. Patent Number	Expiration Date
5,674,895 (the '895 patent)	November 22, 2015
5,840,754 (the '754 patent)	November 22, 2015
5,912,268 (the '268 patent)	November 22, 2015
6,124,355 (the '355 patent)	November 22, 2015
6,262,115 (the '115 patent)	November 22, 2015

Your ANDA contains paragraph IV patent certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each of these patents are invalid, unenforceable, or will not be infringed by your manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-release Tablets, 10 mg, under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA shall be made effective immediately unless an action was brought against Mylan Pharmaceuticals, Inc. (Mylan) for infringement of one or more of these patents that were the subjects of the paragraph IV certifications. This action must have been brought against Mylan prior to the expiration of 45 days from the date the notice you provided under section 505(j)(2)(B) was received by the NDA/patent holder(s). You have notified the agency that Mylan complied with the requirements of section 505(j)(2)(B) of the Act. As a result, litigation was brought against Mylan in the United States District Court for the Northern District of West Virginia involving your challenge to the '355 patent (Alza Corporation v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., Civil Action No. 1:03-cv-158). We note that Mylan was not sued within the 45-day period on any of the other listed patents.

Therefore, final approval cannot be granted until:

1. a. the expiration of the 30-month period provided for in Section 505(j)(5)(B)(iii)[1] or such shorter or longer period as the court may have ordered, or,

[1] Because information on the '895, '754, '268, '355, and '115 patents was submitted before August 18, 2003, this reference is to a section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) was enacted. See MMA § 1101(c)(3).

b. the date the court decides[2] that the patent(s) is/are invalid or not infringed [see sections 505(j)(5)(B)(iii)(I), (II), and (III) of the Act], or,

c. the '355 patent has expired, and

2. The agency is assured there is no new information that would affect whether final approval should be granted.

To reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your ANDA will be eligible for final approval. Your amendment must provide:

1. A copy of a court decision or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information, and

2. a. updated information related to final-printed labeling or chemistry, manufacturing and controls data, or any other change in the conditions outlined in this abbreviated application, or

b. a statement that no such changes have been made to the application since the date of tentative approval.

This amendment should be submitted even if none of these changes were made, and it should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, at any time prior to the final date of approval the agency may request that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

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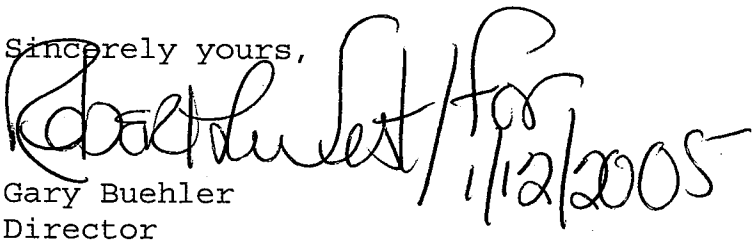
[2] This decision may be either a decision of the district court or the court of appeals, whichever court is the first to decide that the patent is invalid or not infringed.

Any significant changes in the conditions outlined in this abbreviated application and the status of the manufacturing and testing facilities' compliance with current good manufacturing procedures are subject to Agency review before final approval of the application will be made. Such changes should be categorized as representing either "major" or "minor" changes, and they will be reviewed according to OGD policy in effect at the time of receipt. The submission of multiple amendments prior to final approval may also result in a delay in the issuance of the final approval letter.

This drug product may not be marketed without final agency approval under section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug before the effective final approval date is prohibited under section 501 of the Act. Also, until the agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355, and it will not be listed in the "Orange Book".

For further information on the status of this application, or prior to submitting additional amendments, please contact Sarah Park, Project Manager, at 301-827-9275.

Sincerely yours,



Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-644
Division File
Field Copy
HFD-610/R. West
HFD-600/C.Parise
HFD-604/D. Hare
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-623/M.Darj / Mike DARJ 10 Sep 2004
HFD-623/D.Gill/ DSGill 9-10-04, DG 12-7-04
HFD-617/S.Park/ S. Park 9/10/04
HFD-613/D.Catterson/ 11/8/04
HFD-613/J.Grace/ for -VI 12/04

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Robert Lyght
1/12/2005

F/T by

TENTATIVE APPROVAL

Conc satisfactory.
Lloyd Belcher
12/22/04.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

LABELING REVIEWS

TENTATIVE APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-644

Dates of Submission: January 21, 2003, August 20, 2004, September 24, 2004 and October 13, 2004

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 10 mg

BASIS OF TENTATIVE APPROVAL:

TENTATIVE APPROVAL SUMMARY
Container Labels:

(bottles of 100)
Satisfactory in draft as of August 20, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76644\N_000\2004-08-20\Labeling\Proposed BL1.pdf)

(bottles of 500)
Satisfactory in draft as of August 20, 2004 submission.
(Vol. 4.1 and \\Cdsesubogd1\n76644\N_000\2004-08-20\Labeling\Proposed BL2.pdf)

Professional Package Insert Labeling:
Satisfactory in draft as of September 24, 2004 submission.
(Vol. 6.1 and \\Cdsesubogd1\n76644\N_000\2004-10-13\Labeling\Proposed OT.pdf)

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 18-211
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Alza
Date of Approval of NDA Insert and supplement #: June 30, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments

PATENT/ EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			IV
5674895*PED	Nov 22, 2015			
5840754	May 22, 2015			IV
5840754*PED	Nov 22, 2015			
5912268	May 22, 2015			IV
5912268*PED	Nov 22, 2015			
6124355	May 22, 2015	U-378	Method for treating incontinence	IV
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence	

6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV
6262115*PED	Nov 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
020897	April 15, 2006	NPP	New Patient Population	
020897	October 15, 2006	PED	Pediatric Exclusivity	

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	

Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?			
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Ditropan XL by Alza approved June 30, 2004 (NDA 20-897/S013).

2. PATENT/ EXCLUSIVITIES

   See table.

3. MANUFACTURING FACILITY

   Mylan Pharmaceuticals, Inc.
   Morgantown, WV 26505
   (Vol. 1.2, p 000165)

4. STORAGE CONDITIONS:

   NDA - Store at controlled room temperature 15°to 25°C (59°to 77°F).
   ANDA - Store at controlled room temperature 20°to 25°C (68 to 77°F).
   USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

   NDA - Dispense in a tight, light-resistant container as defined in the USP.
   ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

6. INACTIVE INGREDIENTS:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 000060 (Volume 1.1). There is no listing of the ingredients in the (b) (4).

7. PACKAGING CONFIGURATIONS:

   NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.

   ANDA- The 10mg tablets will be packaged in bottles of 100's (75cc) and 500's (200cc) tablets only.

8. CONTAINER/CLOSURE SYSTEM:

1) **The bottles of 100's will be packaged using a 75mL round beige HDPE bottle** from [redacted] (DMF [redacted]. The bottle will be molded using the [redacted] (DMF [redacted].

The closure will be a 38mm beige plastic CRC from [redacted] (DMF [redacted]) and consists of clear [redacted] DMF [redacted] and a beige HDPE outer shell.

The inner seal is a common [redacted]

The desiccant is manufactured by [redacted] (DMF [redacted] and consists of a [redacted] canister containing black activated carbon and silica gel granules.

2) **The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle** from [redacted] (DMF [redacted]. The bottle will be molded using the [redacted] (DMF [redacted].

The closure will be a 45 mm fine-ribbed beige plastic CRC from [redacted] (DMF [redacted] and it consists of clear [redacted] DMF [redacted] shell.

The inner seal is the common [redacted]

The desiccant is manufactured by [redacted] (DMF [redacted] and consists of a [redacted] canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle.
(Vol. 1.2, p. 000337-40)

9. In Mylan's original labeling submission, the Systems Components and Performance section was omitted. Email discussion was exchanged to decide whether or not omitting this section would constitute "same-as" labeling. It was decided that the firm could not omit the section and would have to resubmit an amendment which included this section which described the release system for their product. Wayne Talton was called on September 16, 2004 and he stated that Mylan would resubmit labeling. Below is a copy of the final email sent by John Grace on Thursday September 19, 2004 at 8:38 AM stating our position:

"Mylan's proposal is to eliminate that subsection entirely.
There is no proposed text. -The statement from Wayne Talton is a marketing statement (not a labeling statement) from Mylan's Marketing Department.
I did some checking and found that the approved ANDAs that referenced Procardia XL, which has the same subsection as Ditropan XL, proposed a different statement which would describe the ANDA product. I think this is an "allowable difference" per regs. Eliminating subsection would not meet "same as" requirements.
We will ask Mylan to propose a "System Components and Performance" subsection for their product.

John F. Grace"

Date of Review: October 18, 2004

Dates of Submission: January 21, 2003, August 5, 2004, September 24, 2004 and October 13, 2004

Primary Reviewer: Postelle Birch Date: October 18, 2004

Team Leader: John Grace Date: 10/18/04

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cc: ANDA: 76-644
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAM\MYLAN\LTRS&REV\76-644tap.label.doc
Review

Superseded by AP Summary signed on 12/12/05 (Review of 8/19/05 Amendment)

~~APPROVAL SUMMARY~~

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-644
Dates of Submission: August 19, 2005
Applicant's Name: Mylan Pharmaceuticals, Inc.
Established Name: Oxybutinin Chloride Extended-release Tablets, 10 mg

APPROVAL SUMMARY
Container Labels:

(bottles of 100)
Satisfactory in FPL as of August 19, 2005 submission.
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL1.pdf

(bottles of 500)
Satisfactory in FPL as of August 19, 2005 submission.
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL2.pdf

Professional Package Insert Labeling:
Satisfactory in FPL as of August 19, 2005 submission.
\\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed OT.pdf

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 18-211
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Alza
Date of Approval of NDA Insert and supplement #: June 30, 2004
Has this been verified by the MIS system for the NDA? Yes
Other Comments: BPCA text added

PATENT/ EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File	Labeling impact
5674895	May 22, 2015			IV	none
5674895*PED	Nov 22, 2015				none
5840754	May 22, 2015			IV	none
5840754*PED	Nov 22, 2015				none
5912268	May 22, 2015			IV	none
5912268*PED	Nov 22, 2015				none
6124355	May 22, 2015	U-378	Method for treating incontinence	IV	none
6124355*PED	Nov 22, 2015	U-378	Method for treating incontinence		none
6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV	none
6262115*PED	Nov 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt		none
6919092	May 22, 2015	U-667	Management of incontinence; method for treating incontinence	IV	none
6919092*PED	Nov 22, 2015	U-667	Management of incontinence; method for treating incontinence	IV	none

Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
020897	April 15, 2006	NPP	New Patient Population	BPCA TEXT
020897	October 15, 2006	PED	Pediatric Exclusivity	

FOR THE RECORD:
1. Review based on the labeling of Ditropan XL by Alza approved June 30, 2004 (NDA 20-897/S013). BPCA text added

2. PATENT/ EXCLUSIVITIES: See table.

3. MANUFACTURING FACILITY

Mylan Pharmaceuticals, Inc.
Morgantown, WV 26505
(Vol. 1.2, p 000165)

4. STORAGE CONDITIONS:

NDA - Store at controlled room temperature 15°to 25°C (59°to 77°F).
ANDA - Store at controlled room temperature 20°to 25°C (68 to 77°F).
USP- Preserve in tight, light-resistant containers.

5. DISPENSING RECOMMENDATIONS:

NDA - Dispense in a tight, light-resistant container as defined in the USP.
ANDA - Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

6. INACTIVE INGREDIENTS:

The listing of inactive ingredients in the DESCRIPTION section of the package insert IS NOT consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 000060 (Volume 1.1). There is no listing of the ingredients in the (b) (4)

7. PACKAGING CONFIGURATIONS:

NDA- The 5 mg, 10 mg and 15 mg tablets are packaged in bottles of 100 tablets.

ANDA- The 10mg tablets will be packaged in bottles of 100's (75cc) and 500's (200cc) tablets only.

8. CONTAINER/CLOSURE SYSTEM:

1) The bottles of 100's will be packaged using a 75mL round beige HDPE bottle from (b) (4) (DMF (b) (4). The bottle will be molded using the (b) (4) (DMF (b) (4).

The closure will be a 38mm beige plastic CRC from (b) (4) (DMF (b) (4) and consists of clear (b) (4) DMF (b) (4) and a beige HDPE outer shell.

The inner seal is a common (b) (4)

The desiccant is manufactured by (b) (4) (b) (4) (DMF (b) (4) and consists of a (b) (4) canister containing black activated carbon and silica gel granules.

2) The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle from (b) (4) (DMF (b) (4). The bottle will be molded using the (b) (4) (b) (4) (DMF (b) (4).

The closure will be a 45 mm fine-ribbed beige plastic CRC from (b) (4) (DMF (b) (4) and it consists of clear (b) (4) DMF (b) (4) shell.

The inner seal is the common (b) (4)

The desiccant is manufactured by (b) (4) (b) (4) (DMF (b) (4) and consists of a (b) (4) canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle.
(Vol. 1.2, p. 000337-40)

Date of Review:	September 9, 2005		
Dates of Submission:	August 19, 2005		
Primary Reviewer:	Postelle Birch	Date:	9/9/2005
Team Leader:	John Grace	Date:	9/12/2005

John J Grace 9/12/05

cc: ANDA: 76-644
DUP/DIVISION FILE
HFD-613/PBirch/ (no cc)
V:\FIRMSAMV:\FIRMSAM\MYLAN\LTRS&REV\76644AP.LABEL.doc
Review

Supersedes AP Summary dated 9/12/05 (Review of 8/19/05 Amendment)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-644

Dates of Submission: August 19, 2005

Applicant's Name: Mylan Pharmaceuticals, Inc.

Established Name: Oxybutinin Chloride Extended-release Tablets, 10 mg

BASIS OF APPROVAL:

APPROVAL SUMMARY
Container Labels:

(bottles of 100)
Satisfactory in FPL as of August 19, 2005 *submission.*
(Vol. 10.1 and \\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL1.pdf)

(bottles of 500)
Satisfactory in FPL as of August 19, 2005 *submission.*
(Vol. 10.1 and \\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed BL2.pdf)

Professional Package Insert Labeling:
Satisfactory in FPL as of August 19, 2005 *submission.*
(Vol. 10.1 and \\Cdsesub1\n76644\N_000\2005-08-19\Labeling\Proposed OT.pdf)

Revisions needed post-approval:

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Ditropan XL
NDA Number: 18-211
NDA Drug Name: Oxybutinin Extended-release Tablets
NDA Firm: Alza
Date of Approval of NDA Insert and supplement #: June 30, 2004
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels:
Basis of Approval for the Carton Labeling:
Other Comments

PATENT/ EXCLUSIVITIES

Patent Data –

No	Expiration	Use Code	Use	File
5674895	May 22, 2015			IV
5674895*PED	Nov 22, 2015			
5840754	May 22, 2015			IV
5840754*PED	Nov 22, 2015			
5912268	May 22, 2015			IV
5912268*PED	Nov 22, 2015			
6124355	May 22, 2015	U-378	Method for treating incontinence	IV
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6262115	May 22, 2015	U-393	Management of incontinence, mgt of hormone replacement therapy, treatment of involuntary incontinence, mgt overactive bladder and increasing compliance in such pt	IV
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Exclusivity Data -

Code/sup	Expiration	Use Code	Description	Labeling Impact
020897	April 15, 2006	NPP	New Patient Population	
020897	October 15, 2006	PED	Pediatric Exclusivity	

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N/A
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 26		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			X
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?			X
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?			X
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N/A
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?			
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			X
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			X
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			X

Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?	X		
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?			
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Because of proposed packaging configuration or for any other reason, does this applicant meet fail to meet all of the unprotected conditions of use of referenced by the RLD?			
Does USP have labeling recommendations? If any, does ANDA meet them?			
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?			
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.			
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

NOTES/QUESTIONS TO THE CHEMIST:

FOR THE RECORD:

1. Review based on the labeling of Ditropan XL by Alza approved June 30, 2004 (NDA 20-897/S013).

2. PATENT/ EXCLUSIVITIES

   See table.

3. MANUFACTURING FACILITY

   Mylan Pharmaceuticals, Inc.
   Morgantown, WV 26505
   (Vol. 1.2, p 000165)

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8. CONTAINER/CLOSURE SYSTEM:

1) The bottles of 100's will be packaged using a 75mL round beige HDPE bottle from [redacted] (DMF [redacted]). The bottle will be molded using the [redacted] (DMF [redacted]).

The closure will be a 38mm beige plastic CRC from [redacted] (DMF [redacted] and consists of clear [redacted] DMF [redacted] and a beige HDPE outer shell.

The inner seal is a common [redacted]

The desiccant is manufactured by [redacted] (DMF [redacted] and consists of a [redacted] canister containing black activated carbon and silica gel granules.

2) The bottles of 500's will be packaged using a 200 mL round beige HDPE bottle from [redacted] (DMF [redacted]). The bottle will be molded using the [redacted] (DMF [redacted]).

The closure will be a 45 mm fine-ribbed beige plastic CRC from [redacted] (DMF [redacted] and it consists of clear [redacted] DMF [redacted] shell.

The inner seal is the common [redacted]

The desiccant is manufactured by [redacted] (DMF [redacted] and consists of a [redacted] canister containing black activated carbon and silica gel granules. This is the same as in the 75mL bottle.
(Vol. 1.2, p. 000337-40)

Date of Review: December 6, 2005

Dates of Submission: August 19, 2005

Primary Reviewer: Postelle Birch Date: 12/8/05

Team Leader: John Grace Date: 12/12/05

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cc: ANDA: 76-644
DUP/DIVISION FILE
HFD-613/PBirch/JGrace (no cc)
V:\FIRMSAM\MYLAN\LTRS&REV\76-644ap.label.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

CHEMISTRY REVIEWS

ANDA #76-644

Oxybutynin Chloride Extended Release Tablets, 10 mg

Mylan Pharmaceuticals, Inc.

Robert W. Trimmer, Ph.D.

Chemistry Division I
Branch IV

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-644

2. REVIEW # **1**

3. REVIEW DATE: July 6, 2003

4. REVIEWER: Robert W. Trimmer, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
n/a	July 21, 2003

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Original	01-21-2003

7. NAME & ADDRESS Of APPLICANT:

Name:	Mylan Pharmaceuticals Inc.
Address:	PO Box 4310 781 Chestnut Ridge Road Morgantown, WV 26504-4310
Representative:	Frank Sisto
Telephone:	304-599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN):

9. LEGAL BASIS For SUBMISSION:
505(j)(2)(A)(vii)
Based on RLD, Ditropan XL
(Oxybutynin Chloride Extended Release Tablets, 10 mg) NDA 20-897

10. PHARMACOL. CATEGORY:
antispasmodic, anticholinergic agent

11. DOSAGE FORM: tablets, ER

12. STRENGTH / POTENCY: 10 mg

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

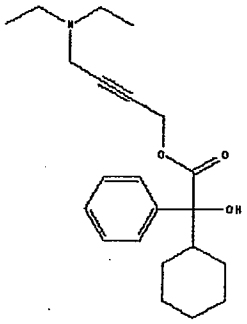
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_x_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Oxybutynin Chloride $C_{22}H_{31}NO_3$. MW 357.4918

4-(Diethylamino)-2-butylnyl-*alpha*-phenylcyclohexaneglycolate hydrochloride.



HCl salt

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Not adequate	06-30-2003 revised 7-2-03	
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			7			The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III			7			"
-							
-							

[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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
n/a		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	pending		
Methods Validation	open		
Labeling	open		D.Caterson
Bioequivalence	open		
Env. Ass.	sat.		
Radiopharmaceutical	n/a		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason below:

The Chemistry Review for ANDA 76-644

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not recommended for approval at this time due to DMF and other issues.

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

n/a

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin chloride drug substance is a USP product. Any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.
Chemical name: 4-(Diethylamino)-2-butylnyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129 deg. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. It spite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4), and (b) (4) NMT (b) (4).

This ER drug product 10mg per dose is not USP. The tablets are peach, film coated, round, biconvex, beveled edged with **M** over **0 10** imprinted in black ink on one side and blank on the other side.

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

The labeling should describe its use. The name given by the innovator is Ditropan Tablets (*HMR, Inc.*).

C. Basis for Approvability or Not-Approval Recommendation

Multiple deficiencies were noted including a non-adequate Type II DMF.

III. Administrative

A. Reviewer's Signature 7-21-03

B. Endorsement Block

ChemistName/Date:	Robert W. Trimmer, Ph.D./
ChemistryTeamLeaderName/Date:	Dave S. Gill, Ph.D./
ProjectManagerName/Date:	Sarah Kim, PM/

C. CC Block

Following this page, 19 pages withheld in full (b)(4)

31. **SAMPLES and RESULTS / *METHODS VALIDATION STATUS*: pending**
The DS, is USP, however, the drug product is not an USP compendial item Method validation by a FDA district laboratory is therefore required, however, the request will be submitted after the issues on assay, **dissolution,** and **impurity** validation parameters have been resolved.

32. **LABELING: open**

33. **ESTABLISHMENT INSPECTION:**
Per EER print Report of July 2nd : pending.

34. **BIOEQUIVALENCE: open**

a. The request for a waiver of *in-vivo* bioequivalence study is to granted by our Division of Bioequivalence.
b. Dissolution data will be compared with DBE's specs.

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:** Sat.

The applicant claims a claim for categorical exclusion under an environmental assessment under 21 CFR 25.31.
The request for exclusion from the requirements for the environmental impact analysis statement was signed by Mr. Sisto.
See page 6062.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-644 APPLICANT: Mylan Pharmaceuticals, Inc.

DRUG PRODUCT: Oxybutynin Chloride Extended Release Tablets, 10 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (b) (4) is deficient. The holder of the DMF has been notified of the deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

2. Regarding your Drug Substance specification:

   a.

   b.

   c.

   (b) (4)

3. Regarding your Drug Product release specifications:

   a.
   A.

   b.

   c.

   (b) (4)

4. Regarding the analytical methods, please provide the LOD data for the process and degradation impurities.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

2. Your bioequivalence information (including dissolution data) are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

3. Please note that methods validation will be scheduled after all issues outlined above in this letter are resolved.

4. A review of the labels and labeling is pending. Any deficiencies found will be sent to you under separate cover.

Sincerely yours,

Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/Robert W. Trimmer, Ph.D. /7/21/03 7-21-03

HFD-623/ Dave S. Gill, Ph.D. /7/21/03 DSGill 7-21-03

HFD-617/S. Kim, Pharm. D. /7/21/03 S.K. 7/21/03

F/T by /sk/7/21/03

V:\FIRMSam\Mylan\LTRS&REV\76644cr01.oxybutynin.rwt.doc

TYPE of LETTER: NOT APPROVABLE - MINOR

ANDA #76-644

Oxybutynin Chloride Extended Release Tablets, 10 mg

Mylan Pharmaceuticals, Inc.

Mike Darj
Office of Generic Drugs
Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-664 (First Generic)

2. REVIEW # 2

3. REVIEW DATE: August 18, 2004
   REVISION DATE: September 10, 2004

4. REVIEWER: Mike Darj, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	21-JAN-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Amendment	02-DEC-2003
Gratuitous Amendment	27-JUL-2004

7. NAME & ADDRESS Of APPLICANT:

Name:	Mylan Pharmaceuticals, Inc.
Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

Executive Summary Section

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Oxybutynin Chloride Extended-release Tablets

9. LEGAL BASIS For SUBMISSION:
505(j)(2)(A)(vii)
Based on RLD, Ditropan Extended Release NDA 20-897 (10 mg)

10. PHARMACOL. CATEGORY:
antispasmodic, anticholinergic agent

11. DOSAGE FORM: tablets, ER

12. STRENGTH / POTENCY: 10 mg

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: Rx

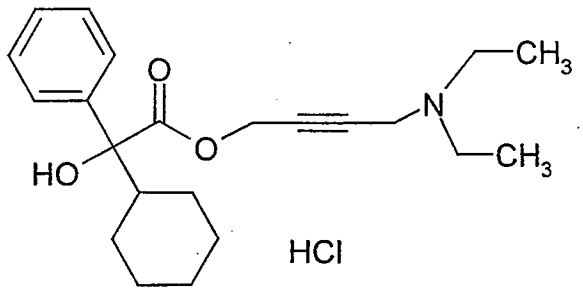
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_x_ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Oxybutynin Chloride $C_{22}H_{31}NO_3.HCl$. FW 393.97

4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride.



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	Dec-2-2004	Reviewed by this reviewer
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			7			The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III			7			"
-							
-							

[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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
n/a		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	acceptable	20Aug03	
Methods Validation	n/a		
Labeling	Acceptable	19Oct2004	P. Birch
Bioequivalence	Acceptable	13Aug2004	P. Nwakama
Env. Assess.	Acceptable		
Radiopharmaceutical	n/a		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes ____ No If no, explain reason below:

The Chemistry Review for ANDA 76-644

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is recommended for approval. See Section II.C.

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

n/a

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin chloride drug substance is a USP product. Any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.
Chemical name: 4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129 deg. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. It spite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4), and (b) (4) NMT (b) (4).

This ER drug product 10mg per dose is not USP. The tablets are peach, film coated, round, biconvex, beveled edged with **M** over **0 10** imprinted in black ink on one side and blank on the other side.

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

The drug product is a tablet that is taken orally.

C. Basis for Approvability or Not-Approval Recommendation

All CMC issues have been successfully addressed.

III. Administrative

A. Reviewer's Signature

07 Dec 2004

B. Endorsement Block
HFD-623/M. Darj, Ph.D., RC/
HFD-623/D. Gill, Ph.D., TL/

F/T by: EW 12/6/04

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Type of Letter: Approvable

C. CC Block
ANDA 76-644
ANDA DUP
DIV FILE
Field Copy

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(b) (4)

[redacted]

30. **MICROBIOLOGY:** n/a

31. **SAMPLES and RESULTS / *METHODS VALIDATION STATUS*:**
n/a

32. LABELING: **Acceptable 19-October-2004**

33. ESTABLISHMENT INSPECTION: Accetpable
EER overall recommendation found acceptable on **20-August-2003**

34. BIOEQUIVALENCE: **Acceptable 8/13/2004**

35. ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION: Sat.
The applicant claims a claim for categorical exclusion under an environmental assessment under 21 CFR 25.31.
The request for exclusion from the requirements for the environmental impact analysis statement was signed by Mr. Sisto.
See page 6062.

cc: ANDA 76-644
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-623/ M. Darj, Ph.D., RC/18Aug2004/10Sep2004/ 07 Dec 04

HFD-623/D. Gill, Ph.D., TL/9-10-04 12-7-04

HFD-617/S. Park, Pharm. D., PM/9-14-04 12/7/04

F/T by: EW 12/6/04

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TYPE of LETTER: APPROVABLE

ANDA #76-644

Oxybutynin Chloride Extended Release Tablets, 10 mg

Mylan Pharmaceuticals, Inc.

Mike Darj
Office of Generic Drugs
Division of Chemistry III

Table of Contents

Chemistry Review Data Sheet

1. ANDA #76-644 (First Generic)

2. REVIEW # 3

3. REVIEW DATES: September 13, 2005 (review of Minor Amendment dated 19Aug2005)
September 19, 2005 (review of Telephone Amendment dated 16Sep2005)
September 21, 2005 (review of Telephone Amendment dated 21Sep2005)
November 14, 2005 (review of Telephone Amendment dated 27Oct2005)

4. REVIEWER: Mike Darj, Ph. D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	21-JAN-2003
Minor Amendment	02-DEC-2003
Gratuitous Amendment	27-JUL-2004
Minor Amendment	19-Aug-2005
Telephone Amendment	16-Sep-2005
Telephone Amendment	21-Sep-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission Reviewed	Document Date
Telephone Amendment	27-Oct-2005

7. NAME & ADDRESS Of APPLICANT:

Name: Mylan Pharmaceuticals, Inc.

Executive Summary Section

Address:	781 Chestnut Ridge Road P.O. Box 4310 Morgantown, WV 26504
Representative:	S. Wayne Talton
Telephone:	(304) 599-2595

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name:
b) Non-Proprietary Name (USAN): Oxybutynin Chloride Extended-release Tablets

9. LEGAL BASIS For SUBMISSION:
505(j)(2)(A)(vii)
Based on RLD, Ditropan Extended Release NDA 20-897 (10 mg)

10. PHARMACOL. CATEGORY:
antispasmodic, anticholinergic agent

11. DOSAGE FORM: tablets, ER

12. STRENGTH / POTENCY: 10 mg (Adults MDD = 30 mg; Pediatrics MDD = 20 mg)

13. ROUTE of ADMINISTRATION: oral

14. Rx/OTC DISPENSED: *Rx*

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

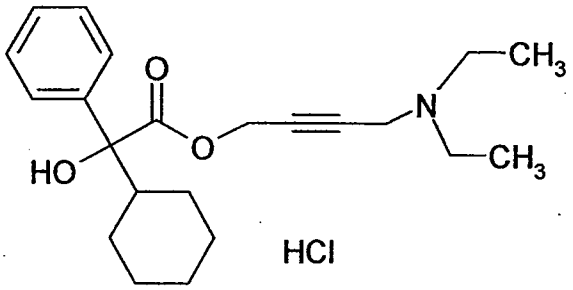
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Oxybutynin Chloride $C_{22}H_{31}NO_3.HCl$. FW 393.97

4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride.



17. RELATED/SUPPORTING DOCUMENTS:

A. **DMFs:**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	3	adequate	19Sep2005	Reviewed by M. Darj
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			7			The component has been previously reviewed & found sat. Numerous ANDAs have been approved using this component.
	III			7			"
-							
-							

[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 is enough data in the application, therefore the DMF did not need to be reviewed)

B. **Other Documents:**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
n/a		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	n/a		
EES	Acceptable	20Aug03	
Methods Validation	n/a	12/12/2005	
Labeling	Acceptable	~~12Aug2005~~	P. Birch
Bioequivalence	Acceptable	13Aug2004	P. Nwakama
Env. Assess.	Acceptable		
Radiopharmaceutical	n/a		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason below:

The review of this minor amendment was expedited as per Sarah Park.

The Chemistry Review for ANDA 76-644

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The ANDA is approvable.

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

n/a

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substance

Oxybutynin chloride drug substance is a USP product. Any previously released DS remaining in inventory 1 year after its original release date or its retest date will be sampled and tested prior to further use. The DS can be recontrolled up to 5 years from date of receipt or up to the manufacturer's expiration date. Materials will be retested at least once per year up to the noted time limit.
Chemical name: 4-(Diethylamino)-2-butynyl-*alpha*-phenylcyclohexaneglycolate hydrochloride. CAS number: 1508-65-2 and MW: 393.97. It is a white to off-white powder melting between 124 to 129 deg. Extensive testing by Mylan via the literature and testing by (b) (4) showed no evidence of polymorphism. This DS is freely soluble in water, very soluble in methanol, slightly soluble in ether, and very slightly soluble in hexane. Despite of it being very soluble in water, Mylan has developed a particle size method and established spec of (b) (4) NMT (b) (4), (b) (4) NMT (b) (4) and (b) (4) NMT (b) (4).

This ER drug product 10mg per dose is not USP. The tablets are peach, film coated, round, biconvex, beveled edged with **M** over **0 10** imprinted in black ink on one side and blank on the other side.

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

The drug product is a tablet that is taken orally.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approvability is based on satisfactory resolution of all deficiencies.

Bioequivalence and labeling sections of ANDA are acceptable.

The drug product, Oxybutynin Chloride ER Tablets, 10 mg can be classified as safe and effective in this review.

III. Administrative

A. Reviewer's Signature

14 Nov 2005

B. Endorsement Block
HFD-630/M. Darj, Ph.D., RC/
HFD-630/D. Gill, Ph.D., TL/

F/T by:

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Type of Letter: Approval

C. CC Block
ANDA 76-644
ANDA DUP
DIV FILE
Field Copy

Following this page, 10 pages withheld in full (b)(4)

30. **MICROBIOLOGY:** n/a

31. **SAMPLES and RESULTS / *METHODS VALIDATION STATUS*:**
n/a

32. **LABELING: Acceptable ~~12Sep2005~~** 12/12/2005

33. **ESTABLISHMENT INSPECTION:** Accetpable
EER overall recommendation found acceptable on **20-August-2003**

34. **BIOEQUIVALENCE: Acceptable 8/13/2004**

35. **ENVIRONMENTAL IMPACT CONSIDERATIONS / CATEGORICAL EXCLUSION:** Sat.
The applicant claims a claim for categorical exclusion under an environmental assessment under 21 CFR 25.31.
The request for exclusion from the requirements for the environmental impact analysis statement was signed by Mr. Sisto.
See page 6062.

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT
None

cc: ANDA 76-644
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-630/ M. Darj, Ph.D., RC/14Nov2005/ 14 NOV 2005

HFD-630/D. Gill, Ph.D., TL/ D Gill 11-20-05

HFD-617/S. Park, Pharm. D., PM/ LMatheny 11/21/05 for

F/T by:

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TYPE of LETTER: Approval

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-644
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	10 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	January 21, 2003
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAM\Mylan\ltrs&rev\76644S.0103

I. Executive Summary

This submission consisted of two (fasting and non-fasting) bioequivalence (BE) studies and dissolution data on the 10 mg strength. The fasting study is a replicate design and the non-fasting study is two-way, crossover study. Both studies are conducted in healthy adult males and females (fasting, n = 36; non-fasting, n = 39). Statistical analyses of the plasma concentration data for oxybutynin and N-desethyloxybutynin in both studies demonstrate bioequivalence.

Oxybutynin results in the fasting study are (point estimate, 90% CI): LAUCT of 0.91, 81.8 -- 100.4%; LAUCI 0.92, 83.1 – 102.2%; and LCmax 0.92, 83.8 – 100.1%.
N-desethyloxybutynin results in the fasting study are (point estimate, 90% CI): LAUCT of 0.91, 84.6 – 97.5%; LAUCI 0.91, 84.9 – 98.5%; and LCmax 0.93, 86.8 – 99.2%.

Oxybutynin results in the non-fasting study are (point estimate, 90% CI): LAUCT of 1.09, 99.8 – 118.5 %; LAUCI 1.11, 101.6 – 120.9%; and LCmax 1.18, 106.8 – **129.4%**.
N-desethyloxybutynin results in the non-fasting study are (point estimate, 90% CI): LAUCT of 0.95, 89.1 – 101.4%; LAUCI 0.97, 90.8 – 103.3%; and LCmax 0.91, 83.5 – 100.1%. The non-fasting study was performed prior to the implementation of the CDER Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies: Study Design, Data Analysis and Labeling.*

The dissolution testing is incomplete, because the firm conducted in a single dissolution medium using the method developed in house. From the bioequivalence point of view, the application is incomplete.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Oxybutynin Chloride ER Tablets
Reference Product	Ditropan® XL
RLD Manufacturer	Alza Pharmaceuticals
NDA No.	20897
RLD Approval Date	December 16, 1998
Indication	Treatment of Overactive Bladder

B. PK/PD Information

Bioavailability	6%
Food Effect	None
Tmax	4 – 6 hours
Metabolism	Extensively metabolized via the enteric and hepatic CYP450 3A4 enzymes. Desethyloxybutynin is an active metabolite.
Excretion	< 0.1% of oxybutynin or N-desethyloxybutynin appears in the urine unchanged
Half-life	12 hours (post-prandial) and 16 hours (fasting)
Relevant OGD or DBE History	This is the first ANDA submitted to the Agency for oxybutynin ER tablets. The Division has responded to 7 control documents [5 CDs (#99-276, (b) (4) 7/12/99; #00-025, (b) (4) 1/14/2000; #00-496 (b) (4) (b) (4) 11/17/2000 and #00-517 (b) (4) 1/28/2000; #01-297, (b) (4) 5/30/2001) on analyte measurement and the remaining 2 inquiries (#02-059, (b) (4) 1/29/2001 and #02-034, (b) (4) 1/11/2002) on *in vivo* bioequivalence and dissolution requirements].

The Division of Bioequivalence (DBE) recommends the measurement in plasma of both oxybutynin and its active metabolite, desethyloxybutynin, using an achiral assay, without measurement of the individual enantiomers, in bioequivalence studies of Oxybutynin HCl Extended Release Tablets.

The Agency's recommendations included that the metabolite, desethyloxybutynin, should be measured because it is formed as a result of presystemic metabolism and contributes meaningfully to efficacy. This is consistent with the CDER Guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations,* March, 2003. Only parent oxybutynin AUC and Cmax data should be analyzed using a confidence interval approach. The metabolite data from the test product should be evaluated for comparability to the metabolite data from the reference product. Since dissolution testing methods for ER products are generally product-specific, firms should establish dissolution methods as a part of product development process. Therefore, firms should conduct dissolution testing using USP apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75,

	and 100 rpm) in different dissolution media (e.g. water, 0.1N HCl and buffers at pH 4.5 and 6.8).
Agency Guidance	CDER Guidance, *Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations,* October 27, 2000.
Drug Specific Issues (if any)	Oxybutynin exhibits dose-dependent, linear pharmacokinetics. The R- and S-isomers of oxybutynin exhibit different pharmacokinetic and pharmacodynamic characteristics. Activity resides primarily with the R-isomer, which is the minor enantiomer. There is no evidence of nonlinear absorption for either enantiomer (OCPB Review of NDA 20-897, 12/15/98).

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	
In vitro dissolution	Yes	1
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Vol. 1.2; pp. 705 - 741		
	Parent	**Metabolite**
Analyte name	Oxybutynin	N-Desethyloxybutynin
Internal Standard	(b) (4)	(b) (4)
Method description	LC/MS	LC/MS
QC range	0.20 to 12.0 ng/mL	0.60 to 36.0 ng/mL
Standard curve range	0.20 to 20.0 ng/mL	0.60 to 60.0 ng/mL
Limit of quantitation	0.20 ng/mL	0.60 ng/mL
Average recovery of Drug (%)	92.64	92.00
Average Recovery of Int. Std (%)	90.51	87.58
Intraday precision range (%CV)	0.42 to 3.48%	1.62 to 3.07%
Intraday accuracy range (%)	93.48 to 101.31%	96.16 to 103.46%
Interday precision range (%CV)	4.55 to 6.08%	2.47 to 8.83%
Interday accuracy range (%)	99.69 to 103.86%	99.91 to 104.27%
Bench-top stability (hrs)	4 hours	4 hours
Stock stability (days)	42 days	31 days
Processed stability (hrs)	96 hours	96 hours
Freeze-thaw stability (cycles)	3	3
Long-term storage stability (days)	203 days	203 days
Dilution integrity	1:1; 101.7% to 111.5%	1:1; 95.5% to 111.9%
Specificity	Yes	Yes
SOPs submitted	Yes	Yes
Bioanalytical method is acceptable	Yes	Yes
20% Chromatograms included (Y/N)	Yes	Yes
Random Selection of Serial Chrom	Yes	Yes

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	OXYB-0262
Study Design	Single-dose, randomized, four-period, two-treatment replicate design
No. of subjects enrolled	36
No. of subjects completing	33
No. of subjects analyzed	33
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 22 Female: 14
Test product	Oxybutynin ER Tablets
Reference product	Ditropan® XL Tablets
Strength tested	10 mg
Dose	2 x 10 mg

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
	Oxybutynin	
AUC0-t	0.91	81.84 – 100.37
AUC∞	0.92	83.14 – 102.25
Cmax	0.92	83.83 – 100.12
	N-desethyl**Oxybutynin**	
AUC0-t	0.91	84.59 – 97.46
AUC∞	0.91	84.88 – 98.53
Cmax	0.93	86.83 – 99.25

Reanalysis of Study Samples Additional information in Appendix, Table 6									
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**				
	Actual number		**% of total assays**		**Actual number**		**% of total assays**		
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**	
N/A (no pharmacokinetic repeats)									
Total									

Did use of recalculated plasma concentration data change study outcome? N/A

There were no PK repeats reported. Subject #33 had a predose N-desethyloxybutynin concentration of 0.654 ng/mL in Period IV which was 1.5% of Cmax. Per FDA guidance, this subject was included in both PK and statistical analyses. 'Whole subject' repeats were performed on Subjects #4, #20 and #34 due to '> 20% of samples unacceptable', '> 20% of samples had poor chromatography' and 'unconfirmed predose', respectively. The reassay values were reported as the final results in accordance with SOP #D416-01, established priori.

Comments on Fasting Study: The fasting study is acceptable.

2. Single-dose Fed Bioequivalence Study

Study No.	OXYB-02109
Study Design	randomized, two-way, single-dose crossover
No. of subjects enrolled	39
No. of subjects completing	35
No. of subjects analyzed	35
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Male: 32 Female: 7
Test product	Oxybutynin ER Tablets
Reference product	Ditropan® XL Tablets
Strength tested	10 mg
Dose	2 x 10 mg

Summary of Statistical Analysis **Additional Information in Appendix, Table 17 and Table 18**		
Parameter	**Point Estimate**	**90% Confidence Interval**
Oxybutynin		
AUC_{0-t}	1.09	99.85 – 118.52
AUC_{∞}	1.11	101.56 – 120.93
C_{max}	1.18	106.85 – **129.41**
N-desethyloxybutynin		
AUC_{0-t}	0.95	89.08 – 101.41
AUC_{∞}	0.97	90.79 – 103.27
C_{max}	0.91	83.46 – 100.07

Reanalysis of Study Samples **Additional information in Appendix, Table 16**								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
N/A (no pharmacokinetic Repeats)								
Total								

Did use of recalculated plasma concentration data change study outcome? N/A

There were no PK repeats reported. Subject #21 had a first measurable oxybutynin concentration of 3.096 ng/mL as Cmax in Period I (Trt A). Per FDA guidance, this subject was included in both PK and statistical analyses. 'Whole subject' repeats were

performed on Subjects #6, #7, #10, #11, #13, #14, #15 and #16 due to 'unacceptable controls'. The reassay values were reported as the final results in accordance with SOP #D416-01, established priori.

Comments on fed study: The non-fasting study is acceptable.

F. Formulation

Location in appendix	Section B, Page 27
Inactive ingredients within IIG Limits (yes or no)	Yes
If no, list ingredients outside of limits	N/A
If a tablet, is the product scored? (yes or no)	No
If yes, which strengths are scored?	N/A
Is scoring of RLD the same as test? (yes or no)	N/A
Formulation is acceptable (yes or no)	Yes
If not acceptable, why?	N/A

G. In Vitro Dissolution

Source of Method	Firm
Medium	Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme Row 2 – 4 (4-, 8- and 16-hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme
Volume (mL)	250 mL
USP Apparatus type	Apparatus 3 (Reciprocating Cylinder)
Rotation (rpm)	25 dips per minute
Firm's proposed specifications	(b) (4) [redacted]
FDA Method:	USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /min; sampling times: 4, 10 and 24 hours.
FDA-recommended specifications	(b) (4) [redacted]
F2 metric calculated (yes or no)	Yes
If no, reason why F2 not calculated	N/A
Method is acceptable (yes or no)	No

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A (one strength)			

F2 metric, test compared to reference	
Strength	F2 metric
10 mg	51

H. Waiver Request(s)

Strengths for which waivers requested	N/A
Regulation cited	N/A
Proportional to strength tested in vivo (yes or no)	N/A
Dissolution is acceptable (yes or no)	No
Waiver granted (yes or no)	N/A

I. Deficiency Comment

The firm conducted dissolution testing in only one medium. The firm should be requested to perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). In addition, the firm should conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 $\pm$ 0.5°C), 50 mL, 30 cycles /minute, sampling times 2, 4, 10 and 24 hours.

J. Recommendations

1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation is acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, are bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, are bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, is incomplete because of the deficiency comment mentioned above.

11/26/2003

Patrick Nwakama, Pharm.D., Branch III, Date signed

11-26-03

Gur Jai Pal Singh, Ph.D., Branch III, Date signed

11/26/03

for Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	OXYB-0262
Study Title	Single-Dose, Fasting Bioequivalence Study
Clinical Site	Kendle International Inc., Morgantown, West Virginia
Principal Investigator	Thomas S. Clark, M.D.
Study/Dosing Dates	Period 1: July 20 – 23, 2002; Period 2: July 27 – 30, 2002 Period 3: August 3 – 6, 2002; Period 4: August 10 – 13, 2002
Analytical Site	Mylan Pharmaceuticals Inc., Morgantown, West Virginia
Analytical Director	(b) (6) Ph.D.
Analysis Dates	September 16 – November 6, 2002
Storage Period	109 days (long-term stability duration: 203 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Oxybutynin ER Tablets	Ditropan® XL Tablets
Manufacturer	Mylan Pharmaceuticals	Alza Corporation
Batch/Lot No.	R1K0797	0112638
Manufacture Date	3/4/02	N/A
Expiration Date	N/A	7/03
Strength	10 mg	10 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Potency	102.9%	100.0%
Content Uniformity	100.7% (RSD 1.2%)	102.4% (RSD 2.6%)
Formulation	See Appendix Section B	
Dose Administered	2 x 10 mg	2 x 10 mg
Route of Administration	Oral	

No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	ABAB: 2,3,5,7,9,11,13,16,19,20,21,24,25,26,29,30, 33,36 BABA: 1,4,6,8,10,12,14,15,17,18,22,23,27,28,31,32, 34,35
Blood Sampling Times	0,1,2,4,5,6,8,10,12,14,16,24,28,36,48 and 60 hours
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	- 70^0C $\pm$ 15^0C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Subjects were monitored throughout the confinement portion of the study. Vital signs were taken prior to dosing and as scheduled post-dosing.

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.00	Male	61.1	Caucasian	61.1
Mean	25.6	Mean	161.2	18-40	97.2	Female	38.9	Afr.Amer.	11.1
SD	5.8	SD	24.9	41-64	2.8			Hispanic	13.9
Range	19 - 44	Range	108 - 212	65-75	0.00			Asian	11.1
				>75	0.00			Other	2.8

Study Results

Table 2 Dropout Information

Subject No	Subject #27	Subject #18	Subject #23
Reason	Adverse Event (vomiting)	Personal reasons	Adverse Event (sore throat and earache)
Period	After Period I	Prior to Period II	Prior to Period II
Replacement	No	No	No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Vomiting		1
Headache	1	2
Nausea		2
Mid-chest Discomfort		1
Loose Stool		1
Abdominal Pain	1	2
Total:	**2**	**9**

Comments: *(on adverse events)*

Compared with the test product, there were about four times more adverse events with the reference product. All events were reported as mild in severity.

Table 4 Protocol Deviations

There were 17 deviations (10 sampling time delays $\leq$ 1 hour and 7 'no show' for blood draws). Actual sampling times were used for statistical and PK analyses. The deviations are not significant to compromise the integrity of the study.

Table 5 Assay Validation – Within Study

Vol. 1.2; pp 271 – 272 and pp 431 - 476		
	Parent	Metabolite
QC Conc. (ng/mL)	0.3 – 12.0 ng/mL	0.9 – 36.0 ng/mL
Inter day Precision (%CV)	0.8 – 9.0 %	1.4 – 13.4%
Inter day Accuracy (%)	100.3 – 103.8%	99.2 – 104.1%
Cal. Standards Conc. (ng/mL)	0.20 – 20.0 ng/mL	0.60 – 60.0 ng/mL
Inter day Precision (%CV)	2.1 – 4.4%	2.0 – 4.3%
Inter day Accuracy (%)	94.9 – 102.8%	96.8 – 101.9%
Linearity Range	0.99470	0.99552

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
D-400-01	8/24/99	Reassay or Reinjection of Clinical Samples
D-416-01	6/18/02	Reassay of Whole Subjects

Comments on repeat assays:

There were no PK repeats. 'Whole subject' repeats were performed on Subjects #4, #20 and #34 due to '> 20% of samples unacceptable', '> 20% of samples had poor chromatography' and 'unconfirmed predose', respectively. The reassay values were reported as the final results in accordance with SOP #D416-01, established priori. The reviewer agrees with the outcome of the repeat assays.

Comments on Within-Study Validation: The within study validation is complete.

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 10 and Figure 1

Oxybutynin

Parameter	Test (Replicate 1)		Test (Replicate 2)		Ref (Replicate 1)		Ref (Replicate 2)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUC_{0-t}	152.31	81.33	156.11	58.84	146.41	76.47	145.76	65.56
AUC_{∞}	184.55	78.06	168.60	62.24	158.49	78.57	159.53	72.47
C_{max}	7.05	70.47	7.62	53.24	7.10	67.99	6.73	51.71
T_{max}	18.12	40.40	13.39	29.22	16.97	45.07	12.76	36.82
$T_{1/2}$	16.06	47.41	13.72	36.44	13.81	36.58	14.18	33.08
k_{el}	0.05	35.28	0.060	51.27	0.06	43.05	0.06	44.51

N-desethyl Oxybutynin

Parameter	Test (Replicate 1)		Test (Replicate 2)		Ref (Replicate 1)		Ref (Replicate 2)	
	Mean	%CV	Mean	%CV	Mean	%CV	Mean	%CV
AUC_{0-t}	662.76	75.92	694.46	58.38	639.21	68.84	665.59	62.51
AUC_{∞}	744.83	79.85	723.15	63.81	702.18	71.16	716.65	70.95
C_{max}	29.84	49.92	31.86	42.91	29.56	48.22	29.99	39.51
T_{max}	10.61	85.18	12.15	37.61	13.41	70.94	10.03	51.17
$T_{1/2}$	8.26	46.65	8.73	49.72	9.53	46.07	8.63	45.59
k_{el}	0.10	43.01	0.10	51.43	0.09	51.31	0.09	44.60

Arithmetic Mean (Combined Replicates) Pharmacokinetic Parameters

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
			Oxybutynin			
AUC0-t	ng*hr/mL	149.40	78.5	150.94	61.7	0.99
AUC∞	ng*hr/mL	170.84	78.2	164.13	66.7	1.04
Cmax	ng/mL	7.08	68.7	7.18	52.6	0.99
Tmax	hr	17.55	42.23	13.08	32.87	1.34
T1/2	hr	14.88	43.28	13.95	34.48	1.07
kel	hr^{-1}	0.05	40.37	0.06	48.28	0.83
			N-desethyl Oxybutynin			
AUC0-t	ng*hr/mL	651.17	72.1	680.02	59.9	0.96
AUC∞	ng*hr/mL	723.51	75.3	719.95	66.9	1.00
Cmax	ng/mL	29.70	48.7	30.92	41.2	0.96
Tmax	hr	11.98	77.65	11.09	44.54	1.08
T1/2	hr	8.89	46.55	8.68	47.35	1.02
kel	hr^{-1}	0.10	44.90	0.10	48.48	1.00

Table 8 Least Square Geometric Means and 90% Confidence Intervals (Based on Proc Mix Procedure)

Parameter	Test	Reference	T/R	90% CI
		Oxybutynin		
AUC0-t	115.68	127.64	0.91	81.84 – 100.37
AUC∞	126.94	137.68	0.92	83.14 – 102.25
Cmax	5.71	6.23	0.92	83.83 – 100.12
		N-desethyl Oxybutynin		
AUC0-t	540.50	595.32	0.91	84.59 – 97.46
AUC∞	561.99	614.49	0.91	84.88 – 98.53
Cmax	26.74	28.81	0.93	86.83 – 99.25

Table 9 Within Subject Variance: Values as taken from the Covariance Parameter Estimates Table of PROC MIXED output are shown below.

Within Subject Variance	Oxybutynin		N-desethylOxybutynin	
	Test	Reference	Test	Reference
LAUC0-t	0.1874	0.0441	0.0876	0.0231
LAUC∞	0.1710	0.0437	0.0851	0.0251
LCmax	0.1111	0.0607	0.0492	0.0269

Comments: (on pharmacokinetic analysis)

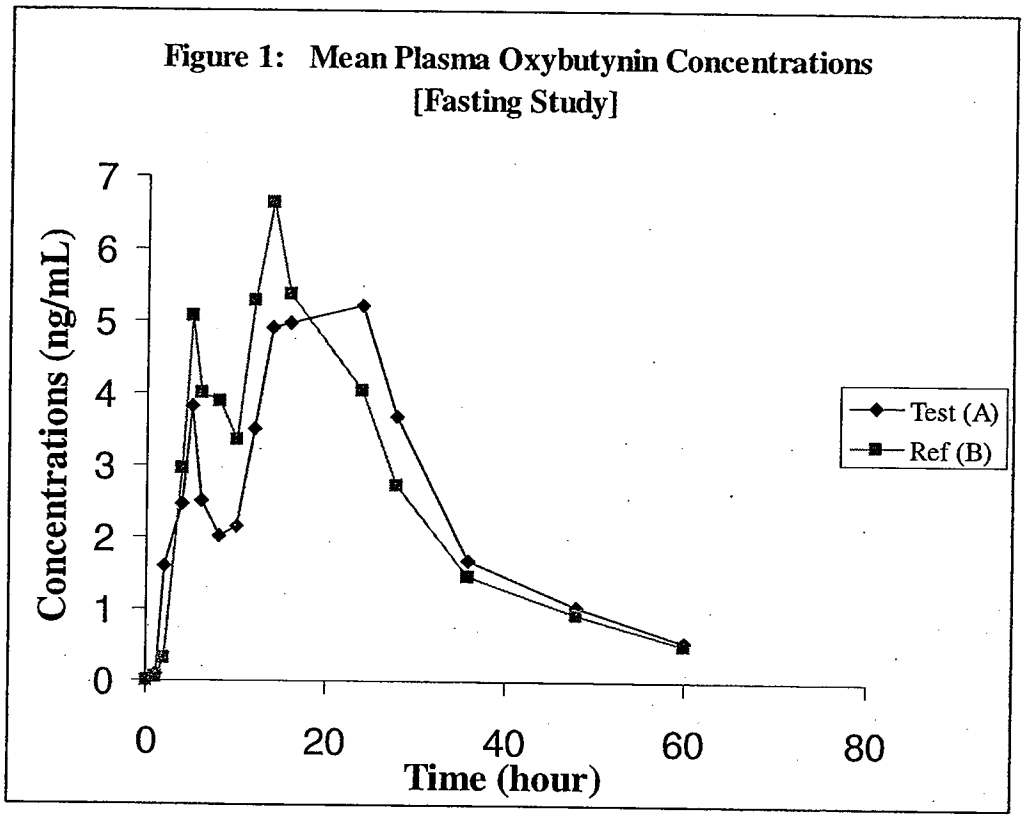
- Ke and AUCi were determined for all subjects.
- Measurable drug concentrations at 0 hr: 1 for N-desethyloxybutynin (subject #33, 1.5% of Cmax). Subject was included in ANOVA analysis. The reviewer agrees with the firm's decision.
- First measurable drug concentration at Cmax: None
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the ln-transformed parameters of AUCt, AUCi, Cmax.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations.

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 10 Mean Plasma Oxybutynin Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study

Time	Test (n= 33)		Reference (n= 33)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0.00	0.00		0.00		0.00
1.00	0.10	253.71	0.05	247.67	2.00
2.00	1.59	121.51	0.31	110.77	5.13
4.00	2.46	88.96	2.95	65.78	0.83
5.00	3.83	66.32	5.07	59.42	0.75
6.00	2.51	62.95	3.99	55.59	0.63
8.00	2.02	90.48	3.89	65.24	0.52
10.00	2.16	93.23	3.36	52.54	0.64
12.00	3.52	80.66	5.29	59.17	0.66
14.00	4.92	86.12	6.65	58.14	0.74
16.00	4.98	96.93	5.37	61.39	0.93
24.00	5.22	84.90	4.05	64.71	1.29
28.00	3.70	84.87	2.73	67.94	1.35
36.00	1.68	103.66	1.47	90.08	1.14
48.00	1.04	119.55	0.94	117.43	1.11
60.00	0.56	117.93	0.51	125.65	1.10

Figure 1 Mean Plasma Oxybutynin Concentrations (ng/mL), Single-Dose Fasting Bioequivalence Study



2. Single-dose Fed Bioequivalence Study

Study Information	
Study Number	OXYB-02109
Study Title	Single-Dose, Non-Fasting Bioequivalence Study
Clinical Site	Kendle International Inc., Morgantown, West Virginia
Principal Investigator	Thomas S. Clark, M.D.
Study/Dosing Dates	Group A Period 1: October 28 – 31, 2002; Period 2: Nov. 4 - 7 , 2002 Group B Period 1: Nov. 2 - 5, 2002; Period 2: Nov. 9 – 12, 2002
Analytical Site	Mylan Pharmaceuticals Inc., Morgantown, West Virginia
Analytical Director	(b) (6) Ph.D.
Analysis Dates	November 12 – 27, 2002
Storage Period	30 days (long-term stability: 203 days)

Treatment ID	A	B
Test or Reference	Test	Reference
Product Name	Oxybutynin ER Tablets	Ditropan® XL Tablets
Manufacturer	Mylan Pharmaceuticals	Alza Corporation
Batch/Lot No.	R1K0797	0112638
Manufacture Date	3/4/02	N/A
Expiration Date	N/A	7/03
Strength	10 mg	10 mg
Dosage Form	Tablets	Tablets
Batch Size	(b) (4)	N/A
Potency	102.9%	100.0%
Content Uniformity	100.7% (RSD 1.2%)	102.4% (RSD 2.6%)
Formulation	See Appendix Section B	
Dose Administered	2 x 10 mg	2 x 10 mg
Route of Administration	Orally (after administration of the OGD-recommended standardized breakfast)	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	2
Washout Period	7 days
Randomization Scheme	AB: 3,4,5,7,9,12,13,16,17,18,22,24,25,28,30,32,34, 35, 37,39 BA: 1,2,6,8,10,11,14,15,19,20,21,23,26,27,29,31, 33, 36,38
Blood Sampling Times	0,1,2,4,5,6,8,10,12,14,16,24,28,36,48 and 60 hours
Blood Volume Collected/Sample	1 x 7 mL
Blood Sample Processing/Storage	- 70^0C $\pm$ 15^0C
IRB Approval	Yes
Informed Consent	Yes
Subjects Demographics	See Table 11
Length of Fasting	10 hours
Length of Confinement	34 hours
Safety Monitoring	Same as Fasting Study

Table 11 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0.00	Male	82.05	Caucasian	76.9
Mean	24.62	Mean	170.62	18-40	97.44	Female	17.95	Afr.Amer.	15.4
SD	6.84	SD	22.59	41-64	2.56			Hispanic	2.6
Range	19 - 56	Range	123 - 215	65-75	0.00			Asian	5.1
				>75	0.00			Other	0.00

Study Results

Table 12 Dropout Information

Subject No	Subject #39	Subject #9	Subject #18	Subject #4
Reason	Adverse Experience	Personal Reasons	(+) Pregnancy	Personal Reasons
Period	Period I	Period II	Period II	Period II
Replacement	No	No	No	No

Table 13 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Vomiting	1	0
Headache	3	1
Nausea	2	0
Total:	**6**	**1**

Comments: *(on adverse events)*

There were more adverse events with the test product but all events were reported as mild in severity.

Table 14 Protocol Deviations

There were nine deviations (2 sampling time delays ≤ 1 hour and 7 'no show' for blood draws). Actual sampling times were used for statistical and PK analyses. The deviations are not significant to compromise the integrity of the study.

Table 15 Assay Validation – Within Study

Vol. 1.7; pp 2847 – 2847 and pp 2987 - 3023		
	Parent	Metabolite
QC Conc. (ng/mL)	0.3 – 12.0 ng/mL	0.9 – 36.0 ng/mL
Inter day Precision (%CV)	2.6 – 6.4 %	1.7 – 8.0%
Inter day Accuracy (%)	99.9 – 108.5%	100.7 – 104.1%
Cal. Standards Conc. (ng/mL)	0.20 – 20.0 ng/mL	0.60 – 60.0 ng/mL
Inter day Precision (%CV)	2.0 – 3.5%	2.1 – 4.0%
Inter day Accuracy (%)	94.7 – 103.0%	96.5 – 101.9%
Linearity Range	0.99353	0.99173

Chromatograms: Any interfering peaks? None

Table 16 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
D-400-02	8/24/99	Reassay or Reinjection of Clinical Samples
D-416-01	6/18/02	Ressay of Whole Subjects

Comments on repeat assays:
There were no PK repeats. 'Whole subject' repeats were performed on Subjects #6, #7, #10, #11, #13, #14, #15 and #16 due to 'unacceptable controls'. The reassay values were reported as the final results in accordance with SOP #D416-01, established priori.

The reviewer agrees with the outcome of the repeat assays.

Comments on Within-Study Validation: The within-study validation is acceptable.

Conclusion: Analytical method is acceptable.

Table 17 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 20 and Figure 2

Oxybutynin						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	**%CV**	**Mean**	**% CV**	
AUC0-t	ng*hr/mL	117.57	49.76	110.90	53.83	1.06
AUC∞	ng*hr/mL	127.63	48.66	118.15	53.73	1.08
Cmax	ng/mL	5.88	58.85	4.95	53.96	1.19
Tmax	hr	18.49	36.60	12.34	50.56	1.50
T1/2	hr	12.96	35.96	12.87	36.45	1.01
kel	hr^{-1}	0.06	31.51	0.06	33.55	0.99
N-desethyloxybutynin						
Parameter	**Units**	**Test**		**Reference**		**T/R**
		Mean	**%CV**	**Mean**	**% CV**	
AUC0-t	ng*hr/mL	550.28	40.18	595.35	48.41	0.92
AUC∞	ng*hr/mL	582.86	38.55	608.34	47.92	0.96
Cmax	ng/mL	26.23	40.34	29.84	51.96	0.88
Tmax	hr	16.89	38.77	9.89	35.19	1.71
T1/2	hr	8.11	44.46	7.89	39.36	1.03
kel	hr^{-1}	0.10	37.46	0.10	37.93	1.00

Table 18 Geometric Means and 90% Confidence Intervals

Oxybutynin				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC0-t	106.57	97.96	1.09	99.85 – 118.52
AUC∞	115.80	104.49	1.11	101.56 – 120.93
Cmax	5.17	4.40	1.18	106.85 – **129.41**

N-desethyloxybutynin				
Parameter	**Test**	**Reference**	**T/R**	**90% CI**
AUC0-t	517.54	544.51	0.95	89.08 – 101.41
AUC∞	539.76	557.42	0.97	90.79 – 103.27
Cmax	24.78	27.11	0.91	83.46 – 100.07

Table 19 Additional Study Information

Oxybutynin		
Root mean square error, AUC0-t	0.2110	
Root mean square error, AUC∞	0.2147	
Root mean square error, Cmax	0.2358	
mean ratio AUC0-t/AUC∞	**T** = 0.93	**R** = 0.94
Range of values, ratio AUC0-t/AUC∞	**T** = 0.75 – 0.97	**R** = 0.86 – 0.98

N-desethyloxybutynin		
Root mean square error, AUC0-t	0.1597	
Root mean square error, AUC∞	0.1583	
Root mean square error, Cmax	0.2234	
mean ratio AUC0-t/AUC∞	**T** = 0.97	**R** = 0.98
Range of values, ratio AUC0-t/AUC∞	T = 0.86 – 0.99	**R** = 0.93 – 0.99

Comments: (on pharmacokinetic analysis)

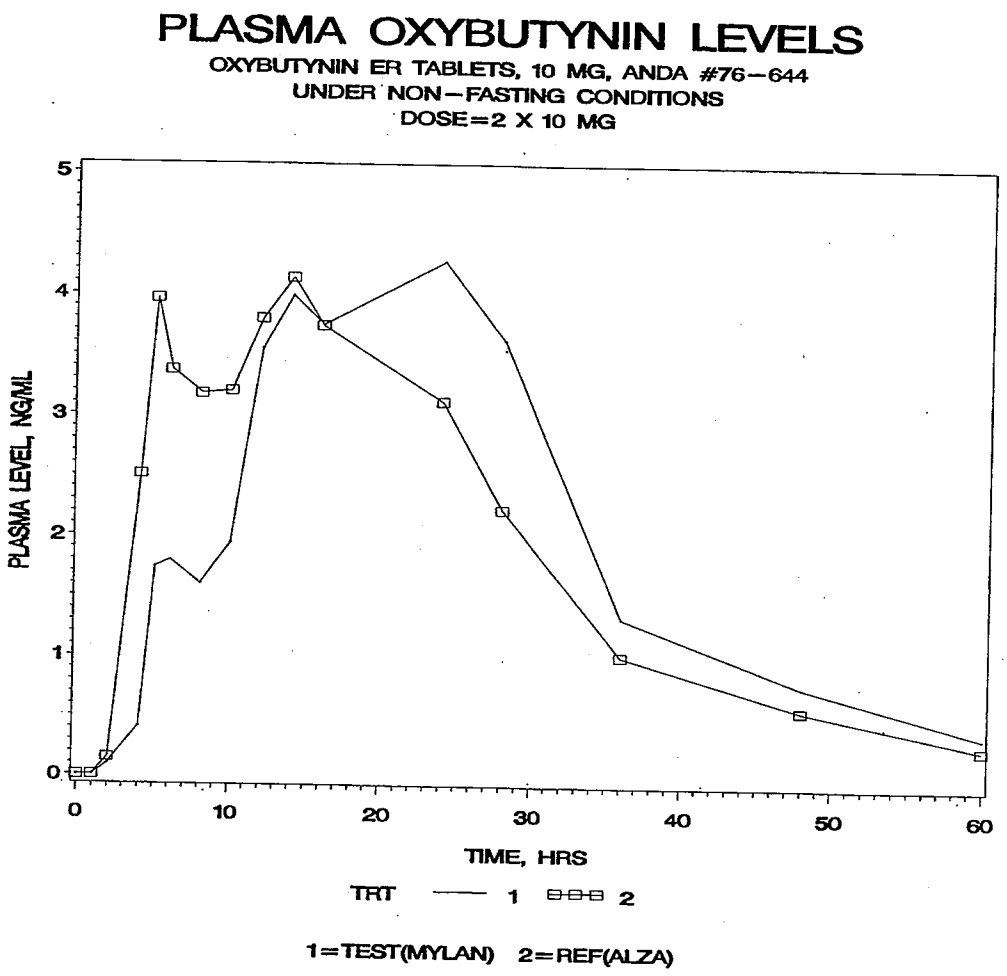
- Ke and AUCi were determined for all subjects.
- Measurable drug concentrations at 0 hr: None
- First measurable drug concentration at Cmax: 1 for oxybutynin (3.096 ng/mL, Subject #21 with trt A). Subject was included in ANOVA analysis. The reviewer agrees with the firm's decision.
- Were there statistically significant sequence or period effects? No
- The 90% confidence intervals are within the acceptable limits of 80-125% for the ln-transformed parameters of AUCt, AUCi, Cmax.
- The pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with those of the firm.
- The subjects were dosed in two groups. The reviewer analyzed submitted data for group effects using model *GRP SEQ SEQ*GRP SUBJ (SEQ*GRP) PER (GRP) TRT TRT*GRP.* There was no significant *TRT*GRP* interaction noted for any of the pharmacokinetic parameters. Therefore, this term was dropped from subsequent analyses.

Conclusion: The single-dose fed bioequivalence study is acceptable.

Table 20 Mean Oxybutynin Plasma Concentrations, Single-Dose Fed Bioequivalence Study

TIME	Test (n =)		Reference (n =)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0.00		0.00		
1	0.00	.	0.00	.	.
2	0.09	415.51	0.15	132.14	0.63
4	0.41	179.20	2.51	69.93	0.16
5	1.74	105.02	3.96	57.27	0.44
6	1.80	114.34	3.37	63.91	0.53
8	1.60	94.41	3.18	82.65	0.50
10	1.94	78.33	3.20	82.22	0.61
12	3.55	58.78	3.80	61.16	0.93
14	3.99	53.55	4.14	52.06	0.96
16	3.75	52.94	3.74	61.78	1.00
24	4.28	81.52	3.12	69.83	1.37
28	3.63	61.62	2.23	53.41	1.63
36	1.34	60.74	1.02	54.52	1.31
48	0.77	75.97	0.58	64.11	1.34
60	0.37	77.80	0.27	92.35	1.38

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

Ingredients	Amount (mg) / tablet	%w/w
Oxybutynin Chloride	10.00	4.53
Povidone, USP	(b) (4)	
Dibasic Calcium Phosphate USP, Anhydrous		
Hydroxypropyl Methylcellulose, NF		
Magnesium Stearate, NF		
Colloidal Silicon Dioxide, NF		
(b) (4)		
Methacrylic Acid Copolymer Dispersion, NF		
Talc USP, (b) (4)		
Triethyl Citrate, NF		
Polysorbate 80, NF		
Sodium Hydroxide, NF		
(b) (4)		
Imprinting Ink (b) (4)		
Total (b) (4) ***Weight***	***220.5***	100.0

C. Dissolution Data

Table 1

Sampling Time (hours)	Oxybutynin ER Tablets 10 mg Lot No. R1K0797			Ditropan® XL Tablets 10 mg Lot No. 0112638		
	Mean	%CV	Range	Mean	%CV	Range
2	0	233.6	(b) (4)	1	22.0	(b) (4)
4	17	4.9		12	15.7	
8	48	2.7		36	11.9	
16	95	1.7		81	5.1	

Figure 3 Dissolution Profiles (*optional*)

D. Consult Reviews

None

E. SAS Output

	Parent	Metabolite
Fasting	 OXYBUTYNIN7664 4fast_output.txt	 DESETHYLoxybuty nin76644fast_outp
Non-Fasting	 OXYBUTYNIN7664 4fed_output.txt	 DESETHYLoxybuty nin76644fed_outp

BIOEQUIVALENCY DEFICIENCY COMMENT TO BE PROVIDED TO THE APPLICANT

ANDA: 76-644 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

You have conducted dissolution testing only in one medium. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminating. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 $\pm$ 0.5°C), 50 mL, 30 cycles /minute. We recommend sampling times of 1, 2, 4, 10 and 24 hours, or until at least 80% of the drut is dissolved.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-644
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama 11/26/2003

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Printed in final on //

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama
HFD-658/ GJP Singh 11-26-03
HFD-650/ S.Mazzella
HFD-650/ D. Conner 11/26/03

BIOEQUIVALENCY - Incomplete Submission Date: January 21, 2003

1. **FASTING STUDY** (STF) Strengths: 10 mg
Clinical: Kendle International Inc. **Outcome: IC**
Analytical: Mylan Pharmaceuticals

2. **FOOD STUDY** (STP) Strength: 10 mg
Clinical: Kendle International Inc. **Outcome: IC**
Analytical: Mylan Pharmaceuticals

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-644
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	10 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	January 21, 2003
Amendment Date(s)	February 18, 2004
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAM\Mylan\ltrs&rev\76644a0204

I. Executive Summary

Mylan Pharmaceuticals previously submitted fasting and non-fasting bioequivalence (BE) studies for the 10 mg tablet on January 21, 2003. Both BE studies were found acceptable based on the following results.

Oxybutynin results in the fasting study were (point estimate, 90% CI): LAUCT of 0.91, 81.8 – 100.4%; LAUCI 0.92, 83.1 – 102.2%; and LCmax 0.92, 83.8 – 100.1%. N-desethyloxybutynin results in the fasting study were (point estimate, 90% CI): LAUCT of 0.91, 84.6 – 97.5%; LAUCI 0.91, 84.9 – 98.5%; and LCmax 0.93, 86.8 – 99.2%. Oxybutynin results in the non-fasting study were (point estimate, 90% CI): LAUCT of 1.09, 99.8 – 118.5 %; LAUCI 1.11, 101.6 – 120.9%; and LCmax 1.18, 106.8 – **129.4%**. N-desethyloxybutynin results in the non-fasting study were (point estimate, 90% CI): LAUCT of 0.95, 89.1 – 101.4%; LAUCI 0.97, 90.8 – 103.3%; and LCmax 0.91, 83.5 – 100.1%. The non-fasting study was performed prior to the implementation of the fed BE guidance and the study met the acceptance standards (ratio of means) in place at that time.

The dissolution testing was found incomplete because only one medium (simulated gastric and intestinal fluids without enzyme) was employed using an in-house dissolution method.

In this amendment, the firm has submitted additional dissolution data using the methods requested by the DBE. The test product now meets the FDA dissolution specifications. However, the application is incomplete pending the firm's acceptance of the DBE recommended dissolution method and specification.

Background:

January 21, 2003 - Mylan Pharmaceuticals submitted original ANDA (76644) containing two BE (fasting and non-fasting) studies for its Oxybutynin ER Tablets. The BE studies were found acceptable. The dissolution testing was not conducted in at least three dissolution media as required for modified release drug products. Therefore, the application was found incomplete. A deficiency letter was sent on December 8, 2003, requesting the firm to conduct additional dissolution testing.

February 18, 2004 - the firm submitted additional dissolution data as an amendment to the ANDA.

FDA Deficiency Comment:

You have conducted dissolution testing only in one medium. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminating. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /minute. We recommend sampling times 1, 2, 4, 10 and 24 hours, or until at least 80% of the drug is dissolved.

Firm's Response:

Mylan started the comparative dissolution testing by using the recommended media with the highest recommended paddle speed (100 rpm). The only medium in which the test product exhibited drug release was pH 6.8 buffer (Table I). The firm felt this was expected since the test product utilizes an enteric coating that does not facilitate drug release at pH values less than 5.5. Consequently, the firm stopped further dissolution testing in the other recommended dissolution media, water, 0.1 N HCl, and pH 4.5 buffer. Using pH 6.8 buffer, the firm also conducted testing with paddle at 50 and 75 rpm and basket at 100 rpm (Table II). The firm did not conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles /minute because the test product will not exhibit drug release at pH 1.2.

Mylan claims that dissolution of its test product occurs only in pH 6.8 buffer with paddle or basket because of [redacted] (b) (4) However, the firm did not propose specifications for percent dissolution.

Reviewer's Comments:

The reviewer and Dr. Tran, the DBE dissolution focal point agree that the test product exhibited the best dissolution profile in 900 mL phosphate buffer pH 6.8, Basket at 100 rpm (see e-mail attachment).

Recommendations

1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, is now acceptable.

   The dissolution testing should be conducted in 900 mL, pH 6.8 phosphate buffer using USP Apparatus I (Basket) at 100 rpm. The test product should meet the following specifications:

   1 hr: NMT (b) (4)
   4 hrs: (b) (4)
   10 hrs:
   24 hrs: NLT (b) (4)

Patrick Nwakama, Pharm.D., Branch III, — Date signed 3/15/2004

Gur Jai Pal Singh, Ph.D., Branch III, — Date signed 3-15-04

Barbara M. Davit — 3/16/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Table I

in vitro Dissolution Testing

Drug Name): Oxybutynin Cl ER Tablets, 10 mg Reference Drug: Ditropan® XL
RPM: 100 rpm No. Unit Tested: 12
Tolerance: N/A
Assay Method: N/A

Sampling Times (HOURS)	Test Product: Oxybutynin ER Lot Number: R1K0797 Strength: 10 mg			Reference Product: Ditropan® XL Lot Number: 0330260 Strength: 10 mg		
	MEAN	**RANGE**	**%CV**	**MEAN**	**RANGE**	**%CV**
0.1 N HCl, 900 mL, Paddle @ 100 rpm						
1	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.0	12	(b) (4)	22.3
10	0.0	0.0	0.0	48		14.5
24	0.0	0.0	0.0	94		3.1
Water, 900 mL, Paddle @ 100 rpm						
1	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.0	14	(b) (4)	12.4
10	0.0	0.0	0.0	50		10.0
24	0.0	0.0	0.0	95		2.1
pH 4.5 Acetate buffer, 900 mL, Paddle @ 100 rpm						
1	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0
4	0.0	0.0	0.0	14	(b) (4)	20
10	0.0	0.0	0.0	50		11.3
24	0.0	0.0	0.0	95		3.0
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 100 rpm						
1	3	(b) (4)	19.3	0.0	0.0	0.0
2	7		18.3	1	(b) (4)	107.4
4	15		18.9	12		12.6
10	36		17.9	48		5.7
24	72		12.6	94		1.4

Sampling Times (HOURS)	Test Product: Oxybutynin ER Lot Number: R1K0797 Strength: 10 mg			Reference Product: Ditropan® XL Lot Number: 0330260 Strength: 10 mg		
	MEAN	**RANGE**	**%CV**	**MEAN**	**RANGE**	**%CV**
pH 6.8 Phosphate buffer, 900 mL, Basket @ 100 rpm						
1	5	(b) (4)	15.5	0.0	0.0	0.0
2	10		16.1	1.0	(b) (4)	98.1
4	21		13.8	12		12.0
10	46		8.8	46		8.7
24	96		3.7	93		2.9
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 50 rpm						
1	2	(b) (4)	19.9	0.0	0.0	0.0
2	5		14.3	0.0	(b) (4)	181.7
4	10		7.3	10		24.1
10	26		12.3	44		9.8
24	54		13.1	91		2.1
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 75 rpm						
1	3	(b) (4)	19.0	0.0	0	0.0
2	6		16.4	1.0	(b) (4)	176.0
4	12		16.4	11		21.0
10	29		16.0	45		12.2
24	62		14.8	92		3.6
pH 6.8 Phosphate buffer, 900 mL, Paddle @ 100 rpm						
1	3	(b) (4)	19.3	0.0	0.0	0.0
2	7		18.3	1	(b) (4)	107.4
4	15		18.9	12		12.6
10	36		17.9	48		5.7
24	72		12.6	94		1.4

E-mail Attachment

-----Original Message-----

From: Tran, Nhan L
Sent: Monday, March 01, 2004 9:27 AM
To: Nwakama, Patrick E
Cc: Singh, Gur J P
Subject: DISSOLUTION METHOD FOR OXYBUTYNIN EXTENDED-RELEASE TABLETS

The firm provided enough information for us to make an informed recommendation. Results submitted by the firm indicated that the following method and conditions can be adopted for Mylan's Oxybutynin ER tablets:

USP Apparatus I (Basket) at 100 RPM
900 ml phosphate buffer pH 6.8
Tolerances:
1 hr: NMT (b) (4)
4 hrs: (b) (4)
10 hrs
24 hrs: NLT (b) (4)

Remember, this is only a suggestion. Please discuss this with your TL for his opinion and/or concurrence.

Thanks,

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 76-644 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified.

Please acknowledge that you have accepted the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 hr:	NMT	(b) (4)
4 hrs:		(b) (4)
10 hrs:		
24 hrs:	NLT	(b) (4)

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76-644
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama 3/15/2004

V:\FIRMSAM\Mylan\LTRS&REV\76-644a0204.doc
Printed in final on 3/15/2004

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama
HFD-658/ GJP Singh -3-15-04
HFD-650/ S.Mazzella
HFD-650/ D. Conner 3/15/04

BIOEQUIVALENCE - DEFICIENCY Submission Date: January 21, 2003

STUDY AMENDMENT (STA) Strength: 10 mg
Clinical: Kendle International Inc. **Outcome: IC**
Analytical: Mylan Pharmaceuticals

Outcome Decisions: IC - Incomplete

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76644
Drug Product Name	Oxybutynin Chloride Extended-Release Tablets
Strength	10 mg
Applicant Name	Mylan Pharmaceuticals Inc.
Address	781 Chestnut Ridge Road, Morgantown, WV 26504
Submission Date(s)	June 9, 2004
Amendment Date(s)	N/A
Reviewer	Patrick Nwakama
First Generic	Yes
File Location	V:\firmsAM\Mylan\ltrs&rev\76644a0604

I. Executive Summary

This is a review of a study amendment. Mylan Pharmaceuticals previously submitted acceptable fasting and non-fasting bioequivalence (BE) studies for the 10 mg tablet on January 21, 2003. The application was found incomplete because the dissolution testing was conducted using one medium only (Apparatus 3 [Reciprocating Cylinder] in simulated gastric and intestinal fluids without enzyme). At the request of DBE, the firm submitted an amendment (2/18/2004) containing data of dissolution testing conducted in various media. Subsequently, the DBE recommended the following dissolution method and specifications [900 mL, pH 6.8 Phosphate Buffer, Apparatus I (Basket), 100 rpm; 1 hr: NMT (b) (4) 4 h: (b) (4) 10 h: (b) (4) and 24 h: NLT (b) (4)].

In this amendment, the firm did not accept the above FDA-recommended dissolution method and cited the following reasons: 1) absence of an acid stage challenge to provide control of the test product's functional enteric coating; 2) the bioequivalent test product will not routinely meet the FDA recommended specification; 3) the proposed dissolution method does not allow for maximum attainment of drug release for the test product; and 4) high variability in dissolution is observed with the FDA method. Therefore, the firm proposes retaining its original dissolution method and specifications [Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute; 2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT (b) (4)]. The firm has submitted additional dissolution data generated under varying temperature, humidity and tablet storage conditions using the FDA-recommended method (Phosphate Buffer pH 6.8) along with updated stability data for its proposed dissolution method.

Following the review of the dissolution data submitted in the original application and amendment, the DBE now accepts the firm's proposal to retain its original dissolution method [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] for its 5 mg and 10 mg drug products. However, the firm's proposed specifications are not acceptable. The DBE has modified the dissolution specifications to 2 h: 0 – 10%; 4 h: 10 – 30%; 8 h: 40 – 65% and 16 h: NLT 80%. The application is deficient pending the firm's acceptance of the new specifications recommended by the DBE.

Background:

January 21, 2003 – Mylan Pharmaceuticals submitted original ANDA (76644) containing two BE (fasting and non-fasting) studies for its Oxybutynin ER Tablets. The BE studies were found acceptable. The dissolution testing was not conducted in at least three dissolution media as required for modified release drug products. Therefore, the application was found incomplete. A deficiency letter was sent on December 8, 2003, requesting the firm to conduct additional dissolution testing. *The firm submitted (March 28, 2003) a separate application (ANDA #76702) for its Oxybutynin ER 5 mg Tablets.*

February 18, 2004 – the firm submitted additional data generated from dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (Water, 0.1 N HCl, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer). A significant drug release occurred only in pH 6.8 buffer (paddle or basket) and this was attributed by firm to the unique coating and release mechanism of its drug product. The DBE recommended the following dissolution method and specifications [900 mL, pH 6.8 Phosphate Buffer, Apparatus I (Basket), 100 rpm; 1 hr: NMT (b) (4) 4 h: (b) (4) 10 h: (b) (4) and 24 h: NLT (b) (4)] to the firm.

Current Submission:

FDA Deficiency Comment:

Please acknowledge that you have accepted the following dissolution method and specifications. The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 h: NMT (b) (4)
4 h: (b) (4)
10 h:
24 h: NLT (b) (4)

Firm's Response:

In response to the deficiency letter from the FDA, the firm reviewed the previously submitted drug release results generated using the above FDA recommended dissolution method. The results of the original dissolution data using the FDA recommended method showed that the 5 mg tablet did not meet the L_1 specification criteria for dissolution. Consequently, additional dissolution testing was conducted using the FDA method on different samples, conditions, days and instruments (see Tables I – III). The firm made the following conclusions: 1) the proposed method does not have an acid stage challenge; therefore, no control of the functional enteric coating of Mylan's drug product, 2) Mylan's drug product will not routinely meet the FDA recommended specification for both 5 mg and 10 strengths, 3) the FDA method does not provide full extent of drug release for the Mylan product, and 4) the FDA method has a high level of variability. Based on these conclusions, the firm felt that the FDA recommended method is not a

suitable quality control test for release and stability testing of its drug product. The firm proposes to adopt the dissolution method it submitted with the original application [Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2 - 4 (4 –, 8 – and 16 – hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute] and specifications [2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT (b) (4)] and has provided stability data (at 25° C) for this method.

Reviewer's Comments:

Based on the dissolution data submitted in the original application and this amendment, the firm's proposal to retain its original dissolution method [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] for both the 5 mg and 10 mg strengths of its product is now acceptable. However, the firm's proposed specifications are not acceptable. The reviewer recommends the following modified dissolution specifications of 2 h: 0 – 10%; 4 h: 10 – 30%; 8 h: 40 – 65% and 16 h: NLT 80%.

Recommendations

1. The single-dose, fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrates that under fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

2. The single-dose, non-fasting bioequivalence study conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 10 mg, lot # R1K0797, comparing it to Ditropan® XL Tablets, 10 mg, lot # 0112638 manufactured by Alza Corporation was previously found acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, Mylan's Oxybutynin Chloride ER Tablets, 10 mg, were bioequivalent to the reference product, Ditropan® XL Tablets, 10 mg, manufactured by Alza Corporation.

3. The *in vitro* dissolution testing conducted by Mylan Pharmaceuticals on the test product, Oxybutynin Chloride ER Tablets, 5 mg, [Row 1 (2-hr): pH 1.2 simulated gastric fluid (SGF) w/o enzyme; Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 simulated intestinal fluid (SIF) w/o enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder)] is now acceptable. However, the firm's proposed specifications are not acceptable. The Division of Bioequivalence recommends the following dissolution specifications:

2 hr: 0 – 10%
4 hr: 10 – 30%
8 hr: 40 – 65%
16hr: NLT 80%

7/16/2004

Patrick Nwakama, Pharm.D. Branch III, Date signed

7/16/2004

Yih Chain Huang, Ph.D., Branch III, Date signed

7/16/04

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Table I: in vitro Dissolution Testing

FDA Method [pH 6.8 Phosphate buffer, 900 mL, Basket @ 100 rpm] No. Unit Tested: 12

Sampling Times (hour)	Test Product: Oxybutynin Cl Extended Release Tablets Lot Number: R1K0797 Strength: 10 mg		
	MEAN	RANGE	%CV
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle, stored at warehouse conditions [Date of Assay: 5/19/2004]			
1	4	(b) (4)	4.0
4	17		3.2
10	42		5.1
24	80		3.6
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle, stored at warehouse conditions [Date of Assay: 5/21/2004]			
1	4	(b) (4)	9.0
4	17		13.1
10	42		9.4
24	83		6.8
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle; 25°C /60% R.H. 3 months [Date of Assay: 5/04/2004]			
1	4	(b) (4)	4.1
4	18		4.9
10	42		3.1
24	83		3.2
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle; 25°C /60% R.H. 3 months [Date of Assay: 5/07/2004]			
1	4	(b) (4)	5.5
4	17		5.2
10	43		3.7
24	81		2.9
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 500 count bottle; 25°C /60% R.H. 18 months [Date of Assay: 5/11/2004]			
1	4	(b) (4)	10.4
4	16		5.5
10	41		5.2
24	82		4.6
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 500 count bottle; 25°C /60% R.H. 3 months [Date of Assay: 5/14/2004]			
1	3	(b) (4)	25.5
4	16		9.8
10	41		4.3
24	81		3.7
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle; 40°C /75% R.H. 3 months [Date of Assay: 5/03/2004]			
1	4	(b) (4)	4.3
4	19		6.2
10	44		4.8
24	83		3.8
pH 6.8 Phosphate buffer, 900 mL @ 37°C, Basket @ 100 rpm 100 count bottle; 40°C /75% R.H. 3 months [Date of Assay: 5/20/2004]			
1	4	(b) (4)	3.4
4	18		5.3
10	45		7.6
24	84		4.2

Following this page, 1 page withheld in full (b)(4)

Table III (submitted with the Original application – January 21, 2003)

Firm's Dissolution Method: Row 1 (2–hour): pH 1.2 SGF w/o Enzyme Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 SIF w/o Enzyme; 250 mL Apparatus 3 (Reciprocating Cylinder); 25 dips per minute Specifications (firm proposed): 2 h: (b) (4) 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT (b) (4)						
Sampling Time (hours)	**Oxybutynin ER Tablets 10 mg Lot No. R1K0797**			**Ditropan® XL Tablets 10 mg Lot No. 0112638**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
2	0	**233.6**	(b) (4)	1	22.0	(b) (4)
4	17	4.9		12	15.7	
8	48	2.7		36	11.9	
16	95	1.7		81	5.1	

Table IV (submitted with the Original application (ANDA # 76702) – March 28, 2003)

Firm's Dissolution Method: Row 1 (2–hour): pH 1.2 SGF w/o Enzyme Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 SIF w/o Enzyme; 250 mL Apparatus 3 (Reciprocating Cylinder); 25 dips per minute Specifications (firm proposed): 2 h: (b) (4); 4 h: (b) (4) 8 h: (b) (4) and 16 h: NLT (b) (4)						
Sampling Time (hours)	**Oxybutynin ER Tablets 5 mg Lot No. R1K3865**			**Ditropan® XL Tablets 5 mg Lot No. 0021413**		
	Mean	**RSD**	**Range**	**Mean**	**RSD**	**Range**
2	0	**188.8**	(b) (4)	2	21.7	(b) (4)
4	18	5.6		11	21.8	
8	51	4.7		35	12.2	
16	102	2.0		83	8.1	

4

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #: 76-644	SPONSOR: Mylan Pharmaceuticals, Inc.
DRUG AND DOSAGE FORM:	Oxybutynin Chloride Extended-Release Tablets
STRENGTH(S):	10 mg
STUDIES:	Fasting and Non-Fasting Studies
CLINICAL STUDY SITE(S):	Kendle International Inc.
ANALYTICAL SITE(S):	Mylan Pharmaceuticals

STUDY SUMMARY: The 90% CI for both in vivo bioequivalence studies are within acceptable limits.
DISSOLUTION: The firm accepted DBE-recommended dissolution method.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic __Yes_ New facility _____ For cause ____ Other ____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____ No___X____
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm: Yes _____X_____

PROJECT MANAGER: _____ DATE: _13AUG04___

PRIMARY REVIEWER: PATRICK NWAKAMA BRANCH: III

INITIAL: _____ DATE: 8/13/2004

TEAM LEADER: YIH-CHAIN HUANG BRANCH: III

INITIAL: _____ DATE: 8/13/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL: _____ DATE: 8/13/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076644Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

January 21, 2003

505(j)(2)(A) OK
07-MAR-2003

ELECTRONIC DATA ENCLOSED
BIOEQUIVALENCE DATA ENCLOSED

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG

Dear Mr. Buehler:

Pursuant to section 505(j) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.92 and 314.94, we submit the enclosed abbreviated new drug application for:

Proprietary Name: None
Established Name: Oxybutynin Chloride Extended-release Tablets
This application consists of a total of 27 volumes.
Archival Copy - 12 volumes.
Review Copy - 13 volumes.
Technical Section For Chemistry - 3 volumes.
Technical Section For Pharmacokinetics - 10 volumes.
Analytical Methods - 2 extra copies; 1 volume each.
NOTE: The Technical Section for Pharmacokinetics of the review copy and the archival copy each contains a set of data diskettes for the bioequivalence studies conducted in support of this application.

This application provides for the manufacture of Oxybutynin Chloride Extended-release Tablets, 10mg. Mylan Pharmaceuticals Inc., 781 Chestnut Ridge Road, Morgantown, WV 26505-2730, performs all operations in the manufacture, packaging, and labeling of the drug product.

It should be noted that this Abbreviated New Drug Application has been organized according to the Agency's February 1999 Guidance for Industry - 'Organization of an ANDA'. Pursuant to this guidance, Mylan commits to resolve any issues identified in the methods validation process after approval.

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\SECTIONS 01 THRU 07.doc

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 598-5404
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
Product Development (304) 285-6411
Purchasing (304) 598-5401
Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

As required by 21 CFR 314.94(d)(5), we certify that a true copy of the technical sections of this application, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office. The following Table of Contents and Reader's Guide detail the documentation submitted in support of this application.

All correspondence regarding this application should be directed to the attention of the undersigned at Mylan Pharmaceuticals Inc., P.O. Box 4310, 781 Chestnut Ridge Road, Morgantown WV, 26504-4310. Telephone and facsimile inquiries may also be directed to the undersigned at telephone number (304) 599-2595, extension 6600 and/or facsimile number (304) 285-6407.

Sincerely,

S. Wayne Tucker for,

Frank R. Sisto
Executive Vice President
Regulatory Affairs and Generic Drug Development

FRS/dn

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

JAN 21 2003

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG

U.S. PATENT NOS. 4,519,801
PARAGRAPH II CERTIFICATION

U.S. PATENT NOS. 4,612,008; 4,783,337; 5,082,668; 5,674,895; 5,840,754; 5,912,268; 6,124,355 and 6,262,115
PARAGRAPH IV CERTIFICATION

Dear Mr. Buehler:

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent Nos. 4,612,008; 4,783,337; 5,082,668; 5,674,895; 5,840,754; 5,912,268; 6,124,355 and 6,262,115 are invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of the 10mg Oxybutynin Chloride Extended-Release Tablets, for which this application is submitted.

Mylan also certifies that according to the patent information published by the FDA in that document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" (22nd Edition through Cumulative Supplement 10), there is one additional patent that claims the listed product, Oxybutynin Chloride Extended-Release Tablets, 10mg. The patent number is 4,519,801 and expired January 12, 2003.

Mylan further certifies that according to the exclusivity information published by the FDA in that document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations" 22nd Edition through the tenth Cumulative Supplement thereto, the referenced product was covered by an exclusivity provision (PED) which expired June 16, 2002. In addition, there are Pediatric Exclusivity provisions which expire January 12, 2003, March 16, 2004 and November 22, 2015.

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 599-7284
Human Resources (304) 598-5406
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Quality Control (304) 598-5407
Research & Development (304) 285-6409
Sales & Marketing (304) 598-3232

In addition, pursuant to Section 505(j)(2)(B)(i) of the Federal Food, Drug and Cosmetic Act, Mylan will provide notice to each owner of the patents which are the subject of the certification, or their representatives, and also to the holder of the approved application for the listed drug claimed by said patents. Said notice will comply with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice. Said notice will be provided as set forth in 21 CFR 314.95(b), when Mylan receives from FDA an acknowledgment letter stating that this ANDA is sufficiently complete to permit a substantive review. Further, Mylan commits to amend this application pursuant to 21 CFR 314.95(e) to provide certification that notifications sent to the patent owners and application holder have been received.

Mylan will market its Oxybutynin Chloride Extended-Release Tablets, 10mg upon approval of this application, and resolution of the validity, enforcement, or infringement of U.S. Patent Nos. 4,612,008; 4,783,337; 5,082,668; 5,674,895; 5,840,754; 5,912,268; 6,124,355 and 6,262,115.

Sincerely,

Dawn Beto by JS

Dawn J. Beto, Esq.
Associate General Counsel

M E M O R A N D U M

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

DATE : February 14, 2003

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 14-FEB-2003

SUBJECT: Examination of the bioequivalence study submitted with an ANDA for Oxybutynin Chloride Extended-release Tablets, 10 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to U.S.C. 355 (j)(5)(B)(iv).

Mylan Pharmaceuticals, Inc. has submitted ANDA 76-644 for Oxybutynin Chloride Extended-release Tablets, 10 mg. The ANDA contains a certification pursuant to 21 U.S.C. 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Mylan on January 21, 2003 for its Oxybutynin Chloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76-644 FIRM NAME Mylan Pharmaceuticals Inc.

DRUG NAME Oxybutynin Chloride ER Tablets, 10 mg

DOSAGE FORM Tablets

Requested by:
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

☒ **Study meets statutory requirements**

☐ **Study does NOT meet statutory requirements**
Reason:

☐ **Waiver meets statutory requirements**

☐ **Waiver does NOT meet statutory requirements**
Reason:

RECOMMENDATION: ✔ COMPLETE ___ INCOMPLETE

Reviewed by:
Patrick Nwakama
Reviewer
Date: February 20, 2003

Gur Jai Pal Singh
Team Leader
Date: 2-24-03

for Dale P. Conner
Director, Division of Bioequivalence
Date: 2/25/03

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	X				Fasting and Non-Fasting Studies
Assay Methodology	X				
Procedure SOP	X				
Methods Validation	X				
Study Results Ln/Lin	X				
Adverse Events	X				
IRB Approval	X				
Dissolution Data	X				
Pre-screening of Patients	X				
Chromatograms	X				
Consent Forms	X				
Composition	X				
Summary of Study	X				
Individual Data & Graphs, Linear & Ln	X				
PK/PD Data Disk (or Elec Subm)	X				
Randomization Schedule	X				
Protocol Deviations	X				
Clinical Site	X				
Analytical Site	X				
Study Investigators	X				
Medical Records	X				
Clinical Raw Data	X				
Test Article Inventory	X				

BIO Batch Size	X				(b) (4)
Assay of Active Content Drug	X				102.9%
Content Uniformity	X				100.7% (RSD = 1.2%)
Date of Manufacture	X				02/28/02
Exp. Date of RLD	X				7/03
BioStudy Lot Numbers	X				Test - R1K0797 RLD - 0112638
Statistics	X				
Summary results provided by the firm indicate studies pass BE criteria	X				Firm provided data for both parent drug and metabolite (N-desethyloxybutinin)
Waiver requests for other strengths / supporting data		X			Not Applicable - one (10 mg) strength

Additional Comments regarding the ANDA:

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-644 **FIRM NAME** MYLAN PHARMACEUTICALS, INC.

RELATED APPLICATION(S) NA **FIRST GENERIC?** NA

DRUG NAME: OXYBUTYNIN CHLORIDE
DOSAGE FORM: EXTENDED-RELEASE TABLETS, 10 MG

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random 4 Chem Team Leader: Gill, Dave PM: Kim, Sarah

Labeling Reviewer: Catterson, Debbie Micro Review: NA PD study (Med Ofcr): NA

Letter Date JANUARY 21, 2003	**Received Date** JANUARY 22, 2003
Comments EC 1 YES **On Cards YES** **VOIDING SYMPTOMS/NEUROGENIC BLADDER**	**Therapeutic Code 6050300 RELIEVE**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	
Archival, and Review copies Field Copy Certification (Original Signature) YES, orig sig	
Cover Letter YES	
Table of Contents YES	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX YES, orig sig.	☒
Sec. II	**Basis for Submission** **NDA: 20-897** RLD: DITROPAN XL Firm: ALZA ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒
Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: NOVEMBER 22, 2015 A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement JUNE 16, 2002**	☒

Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ok 2. Active ingredients ok 3. Route of administration ok 4. Dosage Form ok 5. Strength ok	☒
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ok 2. 1 RLD label and 1 RLD container label ok 3. 1 side by side labeling comparison with all differences annotated and explained ok 100s and 500s	☒
Sec. VI	**Bioavailability/Bioequivalence** **1. Financial Certification** (Form FDA 3454) **and Disclosure Statement** (Form 3455) YES **2. Request for Waiver of In-Vivo Study(ies):** NA **3. Formulation data same?** (Comparison of all Strengths) (Ophthalmics, Otics, Topicals Perenterals) NA **4. Lot Numbers of Products used in BE Study(ies):** R1K0797 **5. Study Type:** PK (Continue with the appropriate study type box below)	☒
Study Type	**IN-VIVO PK STUDY(IES)** (i.e., fasting/fed/sprinkle) FED AND FAST a. Study(ies) meets BE criteria (90% CI or 80-125, Cmax, AUC) Yes Fasting AUCt 82 -100 AUCi 83 - 102 Cmax 84 - 100 Fed AUCt - 108 AUCi - 110 Cmax - 117 b. Data Files (Computer Media) Submitted YES c. In-Vitro Dissolution YES VOL 10 PAGE 4959-	☒
Study Type	**IN-VIVO BE STUDY with CLINICAL ENDPOINTS** a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted	☐
Study Type	**TRANSDERMAL DELIVERY SYSTEMS** a. <u>In-Vivo PK Study</u> 1. Study(ies) meet BE Criteria (90% CI or 80-125, Cmax, AUC) 2. In-Vitro Dissolution 3. Data Files (Computer Media) Submitted b. <u>Adhesion Study</u> c. <u>Skin Irritation/Sensitization Study</u>	☐

Study Type	**NASALLY ADMINISTERED DRUG PRODUCTS** a. Solutions (Q1/Q2 sameness): 1. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile) b. Suspensions (Q1/Q2 sameness): 1. In-Vivo PK Study a. Study(ies) meets BE Criteria (90% CI or 80-125, Cmax, AUC) b. Data Files (Computer Media) Submitted 2. In-Vivo BE Study with Clinical EndPoints a. Properly defined BE endpoints (eval. by Clinical Team) b. Summary results meet BE criteria (90% CI within +/- 20% or 80-120) c. Summary results indicate superiority of active treatments (test & reference) over vehicle/placebo ($p<0.05$) (eval. by Clinical Team) d. Data Files (Computer Media) Submitted 3. In-Vitro Studies (Dose/Spray Content Uniformity, Droplet/Drug Particle Size Distrib., Spray Pattern, Plume Geometry, Priming & Repriming, Tail Off Profile)	☐
Study Type	**TOPICAL CORTICOSTEROIDS (VASOCONSTRICTOR STUDIES)** a. Pilot Study (determination of ED50) b. Pivotal Study (study meets BE criteria 90%CI or 80-125)	☐
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ok 2. Inactive ingredients as appropriate ok	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers ok, 6412 b. Type II DMF authorization letters or synthesis ok c. COA(s) specifications and test results from drug substance mfgr(s) ok, pg. 5002, Lot 032a21007 d. Applicant certificate of analysis ok, page 5000 Lot 032a21007 e. Testing specifications and data from drug product manufacturer(s) ok f. Spectra and chromatograms for reference standards and test samples IR and chromatogram, ok g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ok b. Testing specifications (including identification and characterization) ok c. Suppliers' COA (specifications and test results) ok d. Applicant certificate of analysis ok	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ok, page 5151 2. CGMP Certification ok 3. CFN numbers 1110315	☒

Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address ok 2. Functions ok 3. CGMP Certification/GLP ok 4. CFN numbers (b) (4)	☒
Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) ok 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ok 3.If sterile product: Aseptic fill / Terminal sterilization NA 4.Filter validation (if aseptic fill) NA 5. Reprocessing Statement ok (b) (4)	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ok 2. In-process Controls - Specifications and data ok Lot R1K0797 - T - (b) (4) A - (b) (4) P - (b) (4)	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ok 2. Components Specification and Test Data (Type III DMF References) ok 3. Packaging Configuration and Sizes ok 4. Container/Closure Testing ok 5. Source of supply and suppliers address ok	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Testing Specifications and Data ok 2. Certificate of Analysis for Finished Dosage Form ok Lot R1K0797	☒
Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ok 2. Post Approval Commitments ok 3. Expiration Dating Period 24 months 4. Stability Data Submitted ok a. 3 month accelerated stability data ok b. Batch numbers on stability records the same as the test batch ok, Lot R1K0797, 100s and 500s	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ok 2. Finished Dosage Form ok 3. Same lot numbers	☒

Sec. XVII	**Environmental Impact Analysis Statement** ok, orig sig	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other**: 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) 2. Debarment Certification (original signature) YES, orig sig 3. List of Convictions statement (original signature) ok	☒

Reviewing CSO/CST **Beth Fabian-Fritsch** **Date** 03/07/03	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 07-MAR-2003
Duplicate copy sent to bio: (Hold if RF and send when acceptable)	
Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002

ANDA 76-644

Mylan Pharmaceuticals, Inc.
Attention: Frank R. Sisto
781 Chestnut Ridge Road
P.O. Box 4310
Morgantown, WV 26504-4310

MAR 10 2003

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

NAME OF DRUG: Oxybutynin Chloride Extended-release Tablets, 10 mg

DATE OF APPLICATION: January 21, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: January 22, 2003

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Sarah Kim
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-644
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB 07-MAR-2003 date
HFD-615/BFritsch, CSO 3/7/03 date
Word File
V:/FIRMSAM/Mylan/ltrs&rev/76644.ack
FT/
ANDA Acknowledgment Letter!

MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

May 27, 2003

6/5/03 (Nz) • Return Receipt • Copy of Suit CA# 1:03CV

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the above referenced Abbreviated New Drug Application (ANDA), which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a), as it pertains to the Paragraph IV patent certification contained in our original application submitted on January 21, 2003 for Oxybutynin Chloride Extended Release Tablets, 10mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patent, and the holder of the application for the listed drug was served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Alza Corporation. A copy of the documentation evidencing Mylan's service and receipt is enclosed. Alza commenced litigation against Mylan on May 2, 2003.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
MAY 28 2003
OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\PATENT-AMENDMENT-052703.DOC

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

JUL 22 2003

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE
EXTENDED-RELEASE TABLETS, 10MG

U.S. PATENT NOS. 4,612,008; 4,783,337;
5,082,668; 5,674,895; 5,840,754; 5,912,268;
6,124,355, 6,262,115 and 4,519,801
ANDA #76-644

PATENT AMENDMENT

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address exclusivity filings by the holder of the referenced drug, which were filed subsequent to Mylan's original submission.

Mylan certifies that according to the exclusivity information published by the FDA in the document entitled "Approved Drug Products with Therapeutic Equivalence Evaluations", 23rd Edition as updated in the "Electronic Orange Book" published at FDA's web site, the referenced product is covered by a New Patient Population ("NPP") exclusivity provision which expires on April 15, 2006. Mylan is not seeking, in its labeling, approval for the use of the product covered by the NPP exclusivity until such time as the exclusivity period expires. Further, Mylan certifies that the referenced product is covered by a newly granted pediatric exclusivity provision ("PED") which is associated with the NPP and which expires on October 15, 2006. As stated above, Mylan is not seeking, in its labeling, approval for the use of the product covered by the NPP/PED exclusivity until such time as the exclusivity period expires.

The exclusivities identified in the preceding paragraph are in addition to the patent/exclusivity information set forth in Mylan's original submission. All patent and exclusivity information set forth in said original submission remains intact and this amendment is merely an update to reflect newly filed exclusivity data.

Sincerely,

Dawn Beto/eg

Dawn J. Beto, Esq.
Associate General Counsel

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 22, 2003

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment (Attachment A) addresses new exclusivity filings by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which have been listed in the FDA's "Orange Book" subsequent to our original submission. The enclosed information is in addition to what has been previously submitted and comprises an update to reflect the newly filed exclusivity information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
JUL 2 4 2003
OGD/CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\PATENT-AMENDMENT-072203.DOC

Department—Fax Numbers
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Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

December 2, 2003

MINOR AMENDMENT
(CMC INFORMATION ENCLOSED)

RECEIVED
DEC 0 3 2003
OGD/CDER

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 22, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the CMC comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated July 22, 2003 (provided in Attachment L). In response to the Agency's comments of July 22nd, Mylan wishes to amend this application as follows:

A. Deficiencies

FDA COMMENT 1: Drug Master File (b) (4) is deficient. The holder of the DMF has been notified of the deficiencies. Please do not submit a MINOR amendment until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

MYLAN RESPONSE: (b) (4)

FDA COMMENT 2: Regarding your Drug Substance specification:

(b) (4)

MYLAN RESPONSE:

FDA COMMENT 2b:

MYLAN RESPONSE:

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Following this page, 1 page withheld in full (b)(4)

(b) (4)

[redacted]

FDA COMMENT 4: Regarding the analytical methods, please provide the LOD data for the process and degradation impurities.

MYLAN RESPONSE: As requested by the Agency, a copy of the method validation report for Limit of Detection for the Related Compounds method (FP-OXYB10-RC-M) has been provided in Attachment K.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

FDA COMMENT 1: The CGMP compliance of all the facilities listed in your application shall be evaluated by our Office of Compliance and a satisfactory evaluation is required prior to the approval of this application.

MYLAN RESPONSE: Mylan acknowledges that the firms referenced in the application must be in compliance with cGMPs at the time of approval.

FDA COMMENT 2: Your bioequivalence information (including dissolution data) are pending review by the Division of Bioequivalence (DBE). The final Release and Stability Specifications will be based on the recommendations of DBE.

MYLAN RESPONSE: Mylan acknowledges that our bio-equivalency information is pending review and deficiencies will be communicated separately. Mylan will resolve any issues identified by the Division of Bioequivalence at that time.

FDA COMMENT 3: Please note that methods validation will be scheduled after all issues outlined above in this letter are resolved.

MYLAN RESPONSE: Mylan acknowledges that methods validation will be scheduled after all issues are resolved. Mylan will provide the information and samples for methods validation upon request. In accordance with the Agency's February 1999 Guidance to Industry, entitled *Organization of an ANDA*, Mylan hereby commits to resolve any issues identified in the methods validation process during review or after approval.

FDA COMMENT 4: The labeling portion of your submission is under review. Deficiencies, if any, will be communicated to you separately.

MYLAN RESPONSE: Mylan acknowledges that the labeling portion of our submission is under review and deficiencies will be communicated separately.

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

February 18, 2004

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION ENCLOSED)

ORIG AMENDMENT
N/AB

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
RESPONSE TO AGENCY CORRESPONDENCE DATED DECEMBER 8, 2003

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated December 8, 2003 (provided in Attachment C). In response to the Agency's comments of December 8th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

You have conducted dissolution testing only in one medium. Please perform dissolution testing using USP Apparatus I (Basket, 100 rpm) and II (Paddle, 50, 75 and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1 N HCl, and buffers at pH 4.5 and 6.8). It may not be necessary to use the higher paddle speeds with Apparatus II if 50 rpm is adequately discriminating. In addition, please conduct dissolution testing using USP Apparatus VII, Artificial Gastric Fluid w/o Enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles/minute. We recommend sampling times of 1, 2, 4, 10 and 24 hours, or until at least 80% of the drug is dissolved.

MYLAN RESPONSE: As requested, Mylan conducted additional comparative dissolution testing on the 10mg strength of Mylan's Oxybutynin Chloride Extended-release Tablets and Ditropan XL® Tablets.

The Agency requested that Mylan perform dissolution testing using USP Apparatus I (Baskets, 100 rpm) and USP Apparatus II (Paddles, 50, 75, and 100 rpm) in 900 mL of various dissolution media (e.g. Water, 0.1N HCl, and buffers at pH 4.5 and 6.8). Mylan initiated the comparative dissolution study by using the recommended media with the highest paddle rotation rate requested (100 rpm). As presented in Attachment A, the only media in which Mylan's product exhibited drug release was pH 6.8 buffer. This was as expected because Mylan's product uses an enteric coating that does not facilitate drug release at pH values below approximately 5.5. As a result, Mylan discontinued further apparatus studies with water, 0.1 N HCl, and pH 4.5 buffer as dissolution media. The other requested apparatus conditions (baskets @ 100 rpm and paddles @ 50 & 75 rpm) were performed using pH 6.8 buffer as the dissolution medium (refer to Attachment B).

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

The Agency also requested that Mylan conduct dissolution testing using Apparatus VII, Artificial Gastric Fluid w/o enzyme (37.0 ± 0.5°C), 50 mL, 30 cycles/minute. As evidenced in the media study discussed above, Mylan's product will not exhibit drug release at the pH requested in this study (approximate pH 1.2); therefore, this testing was not conducted.

In summary, Mylan performed comparative dissolution testing on the 10mg strength of Mylan's Oxybutynin Chloride Extended-release Tablets and Ditropan XL® Tablets. Due to the coating and release mechanism of Mylan's tablet; Apparatus I and II, with pH 6.8 buffer, were the only testing conditions which resulted in dissolution. Results from this comparative dissolution study between Mylan's product and Ditropan XL® are presented in Attachments A and B.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

BIOEQUIVALENCY AMENDMENT

ANDA 76-644

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAR 19 2004

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on February 18, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended-Release Tablets, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review,** nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

sm

MAR 19 2004

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA: 76-644 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified.

Please acknowledge that you have accepted the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 hr: NMT (b) (4)
4 hrs: (b) (4)
10 hrs:
24 hrs: NLT (b) (4)

Sincerely yours,

Barbara M Savit

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

ORIGINAL

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

June 9, 2004

ORIG AMENDMENT
N/A

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
RESPONSE TO AGENCY CORRESPONDENCE DATED MARCH 19, 2004

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated March 19, 2004 (provided in Attachment A). In response to the Agency's comments of March 19th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiency has been identified:

Please acknowledge that you have accepted the following dissolution method and specifications.

The dissolution testing should be conducted in 900 mL of pH 6.8 Phosphate Buffer using USP apparatus I (Basket) at 100 rpm. The test products should meet the following specifications:

1 hr:	NMT	(b) (4)
4 hrs:		(b) (4)
10hrs:		
24 hrs:	NLT	(b) (4)

MYLAN RESPONSE: Mylan received Minor comment letters from the Division of Bioequivalence on March 19, 2004 and April 10, 2004 for the 10mg (ANDA 76-644) and 5mg (ANDA 76-702) tablet strengths of Oxybutynin Chloride Extended-release Tablets, respectively. A copy of the March 19, 2004 letter is provided in Attachment A. Mylan was requested to update the drug release test and specification for both tablet strengths to the following:

Medium:	pH 6.8 phosphate buffer, 900 mL.		
Apparatus 1:	100 rpm.		
Times:	1, 4, 10, and 24 hours.		
Limits:	1 hour:	NMT	(b) (4)
	4 hours:		(b) (4)
	10 hours		
	24 hours	NLT	(b) (4)

RECEIVED
JUN 10 2004
OGD/CDER

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

In response to the Agency's request, Mylan reviewed the previously submitted drug release results which were generated using the FDA recommended method. The data show that the originally submitted results for the FDA recommended method do not meet L_1 criteria for the 5mg tablet strength (refer to Attachment B). As a result of this observation, a further evaluation of the proposed method was conducted. The 5mg and 10mg tablet strengths were tested using the proposed method on different samples, conditions, days and instruments. The following conclusions were made.

1. The proposed method does not have an acid stage challenge; therefore, no control of Mylan's functional enteric coating is provided.
2. Mylan's product, which is bioequivalent to Ditropan XL®, will not routinely meet the FDA recommended specification for both the 5mg and 10mg strengths.
3. The proposed method does not provide full extent of drug release for the Mylan product.
4. The proposed method has a high level of variability (Refer to Attachments B, C and D).

Based on these conclusions, the FDA recommended method is not considered to be a suitable quality control test for release and stability testing of Mylan's Oxybutynin Chloride Extended-release Tablets 5mg and 10mg. Mylan recommends that we retain the drug release test and specifications originally submitted in Mylan's ANDAs as described below.

Medium:	Row 1: pH 1.2 Simulated Gastric Fluid, without enzymes; 250 mL. Rows 2–4: pH 6.8 Simulated Intestinal Fluid, without enzymes; 250 mL.	
Apparatus 3:	25 dips per minute.	
Times:	2, 4, 8, and 16 hours	
Limits:	2 hours:	(b) (4)
	4 hours:	
	8 hours	
	16 hours	NLT (b) (4)

Based on the cumulative data, the Mylan ANDA method produces reproducible results, provides an acid challenge test, and achieves a full drug release of the product. Updated room temperature stability data through 18 months using the ANDA method for drug release for Oxybutynin Chloride Extended-release Tablets, 10mg (Lot R1K0797) is provided in Attachment E.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Executive Director
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Sarah Park, Project Manager

BIOEQUIVALENCY AMENDMENT

ANDA 76-644

JUL 2 0 2004

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Mylan Pharmaceuticals, Inc. TEL: 304-599-2595

ATTN: S. Wayne Talton FAX: 304-285-6407

FROM: Steven Mazzella PROJECT MANAGER: 301-827-5847

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 9, 2004, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Oxybutynin Chloride Extended Release Tablets, 10 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES TO BE PROVIDED TO THE APPLICANT

ANDA: 76-644 APPLICANT: Mylan Pharmaceuticals

DRUG PRODUCT: Oxybutynin Chloride ER Tablets, 10 mg

The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Your proposed dissolution method (Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2 – 4 (4 –, 8 – and 16 – hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250 mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute) is now acceptable but the proposed dissolution specifications are not acceptable.

2. Based on the data submitted, the Division of Bioequivalence recommends the following dissolution specifications:

2 hr:	0 – 10%
4 hr:	10 – 30%
8 hr:	40 – 65%
16hr:	NLT 80%

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs

CC: ANDA 76644
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-658/ P.Nwakama 7/16/2004

V:\FIRMSAM\Mylan\LTRS&REV\76644a0604.doc
Printed in final on 7/16/2004

Endorsements: (Final with Dates)
HFD-658/ P.Nwakama
HFD-658/ YC Huang 7/16/2004
HFD-650/ S.Mazzella
HFD-650/ D. Conner 7/16/04

BIOEQUIVALENCE - DEFICIENCIES Submission Date: June 9, 2004

STUDY AMENDMENT (STA) OIC

Strength: 10 mg
Outcome: IC

Outcome Decisions: IC - Incomplete

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 27, 2004

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE AMENDMENT
(CMC INFORMATION ENCLOSED)
OGB AMENDMENT
N/A-E

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
RESPONSE TO AGENCY CORRESPONDENCE DATED JULY 20, 2004

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the bioequivalence comments pertaining to this application which were provided to Mylan by facsimile in correspondence dated July 20, 2004 (provided in Attachment D). In response to the Agency's comments of July 20th, Mylan wishes to amend this application as follows:

FDA COMMENT 1: The Division of Bioequivalence has completed its review of your submission acknowledged on the cover sheet and the following deficiencies have been identified:

1. Your proposed dissolution method (Row 1 (2-hour): pH 1.2 Simulated Gastric Fluid w/o Enzyme; Rows 2-4 (4-, 8- and 16-hour): pH 6.8 Simulated Intestinal Fluid w/o Enzyme; 250mL; Apparatus 3 (Reciprocating Cylinder); 25 dips per minute) is now acceptable but the proposed dissolution specifications are not acceptable.

2. Based on the data submitted, the Division of Bioequivalence recommends the following dissolution specifications:

2 hr:	0-10%
4 hr:	10-30%
8 hr:	40-65%
16 hr:	NLT 80%

MYLAN RESPONSE: As requested, the recommended dissolution specifications for Oxybutynin Chloride Extended-release Tablets, 10mg have been incorporated into Mylan's stability and quality control programs. Revised finished product specifications, drug release procedure (FP-OXYB10-DR-M) and post-approval stability protocol are provided in Attachments A, B and C, respectively. Please note that a Gratuitous Chemistry Amendment is also being submitted concurrently with this Bioequivalence Amendment under separate cover.

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JUL 2 8 2004
OGD / CDER

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Sarah Park, Project Manager

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 27, 2004

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

GRATUITOUS CHEMISTRY AMENDMENT
(CMC INFORMATION ENCLOSED)
ORIG AMENDMENT
N/A A

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to comments received from the Division of Bioequivalence in correspondence dated July 20, 2004 (provided in Attachment A). The July 20th comments requested a revision in the dissolution specifications for Oxybutynin Chloride Extended-release Tablets, 10mg.

Please note that the dissolution specifications recommended by the Division of Bioequivalence have been incorporated into Mylan's stability and quality control programs. The purpose of this Gratuitous Chemistry Amendment is to update the chemistry portion of our application in accordance with the comments received from the Division of Bioequivalence. A Bioequivalence Amendment is being submitted concurrently with this Chemistry Amendment under separate cover.

Revised finished product specifications with corresponding Certificate of Analysis, a revised drug release procedure (FP-OXYB10-DR-M) and revised post-approval stability protocol are provided in Attachments B, C and D, respectively. In addition, Mylan is submitting updated stability data tables for Oxybutynin Chloride Extended-release Tablets, 10mg which reflect the recommended dissolution specifications (refer to Attachment E).

Pursuant to 21 CFR 314.96(b), we certify that a true copy of the technical sections of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosure

Desk Copy: Sarah Park, Project Manager

RECEIVED
JUL 2 6 2004
OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\GRATUITOUS-AMENDMENT-072704.doc

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 20, 2004

MINOR AMENDMENT
(ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10 mg
ANDA 76-644
(RESPONSE TO AGENCY CORRESPONDENCE DATED AUGUST 13, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the labeling comments pertaining to this application which were provided to Mylan via e-mail on August 13, 2004. In accordance to the Agency's August 13th correspondence, we wish to amend our application by submitting a revised draft outsert. The bottle labels were also updated to revise our storage statement and to incorporate other minor revisions to be consistent with the innovator's container labeling.

In accordance with the Agency's Guidances *Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 10 mg as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word versions of all proposed labeling components. To access these Word files, a bookmark is provided within the pdf version.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's web site for any approved labeling changes.

Should you have any questions regarding this supplement, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: John Grace, Team Leader (Cover letter only)
Debbie Catterson, Labeling Reviewer (Cover letter only)
Division of Labeling and Program Support

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 24, 2004

TELEPHONE AMENDMENT
(ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10 mg
ANDA 76-644
(RESPONSE TO AGENCY TELEPHONE CALL RECEIVED ON SEPTEMBER 16, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our Labeling Amendment submitted on August 20, 2004. Reference is also made to a telephone call received on September 16, 2004 from Ms. Postelle Birch, of your office, in which she requested that Mylan amend our August 20th submission by adding a subsection 'System Components and Performance' to our outsert to describe our Oxybutynin Chloride Extended-release Tablets. The purpose of this amendment is to provide a revised draft outsert incorporating the text pertaining to Mylan's 'System Components and Performance', as requested by the Agency.

In accordance with the Agency's Guidances *Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 10 mg as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word version of our proposed draft outsert. To access this Word file, a bookmark is provided within the pdf version.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's web site for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: Postelle Birch, Labeling Reviewer
Division of Labeling and Program Support

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\TELEPHONE CORRESPONDENCE DATED SEPT 16, 2004. OXYB-RX4.LABELING.doc

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 13, 2004

TELEPHONE AMENDMENT
(ELECTRONIC LABELING INFORMATION ENCLOSED)

Office of Generic Drugs, CDER, FDA
Gary Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10 mg
ANDA 76-644
(RESPONSE TO AGENCY TELEPHONE CALL RECEIVED ON OCTOBER 12, 2004)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our draft labeling included in our Telephone Amendment submitted on September 24, 2004. Reference is also made to a telephone call received on October 12, 2004 from Ms. Postelle Birch, of your office, in which she requested that Mylan amend our September 24th submission by modifying the subsection 'System Components and Performance' in our outsert. The purpose of this amendment is to provide a draft outsert with the revised subsection 'System Components and Performance', as requested by the Agency.

In accordance with the Agency's Guidances *Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets, 10 mg as described in the electronic Table of Contents. As a review aid, Mylan has also included Microsoft Word version of our proposed draft outsert. To access this Word file, a bookmark is provided within the pdf version.

Mylan acknowledges that the Agency may request further changes to the labeling prior to approval. In addition, Mylan may have to revise our labeling pursuant to approved changes for the referenced listed drug. Mylan will monitor FDA's web site for any approved labeling changes.

Should you have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

Desk Copy: Postelle Birch, Labeling Reviewer
Division of Labeling and Program Support

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Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

NAI
PIV cert to
-092
7/26

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 19, 2005

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 19, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
Label Control (800) 848-0463
Legal Services (304) 598-5408
Maintenance & Engineering (304) 598-5411
Medical Unit (304) 598-5445
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Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Associate General Counsel

NAI
Already certified PIV to '092 on
7/19/2005
C. Bina 8/3/2005

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 20, 2005

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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JUL 20 2005
OGD/CDER

RECEIVED
JUL 20 2005
OGD / CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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NAI
Already certified PIV to '092 on
7/19/2005.
C. Bina 8/3/2005

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 21, 2005

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 21, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6401	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0468	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Associate General Counsel

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 22, 2005

PATENT AMENDMENT XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers

Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 22, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

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Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Associate General Counsel

NA1
Already certified PIV to '092 on
7/19/2005.
C. Bina 8/3/2005

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 25, 2005

PATENT AMENDMENT XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
JUL 25 2005
OGD/CDER

G:\PROJECT\ANDA\OXYBUTYNIN CHLORIDE ER\10MG\PATENT-AMENDMENT (NEW PATENT LISTING).DOC

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 26, 2005

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers

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Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
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Corporate Services	(304) 598-5404	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 26, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Associate General Counsel

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 27, 2005

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 598-5404
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 27, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn Beto

Dawn J. Beto, Esq.
Associate General Counsel

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 28, 2005

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to the patent certification information submitted in the original ANDA on January 21, 2003.

This current patent amendment addresses a new patent listing by the holder of the Reference Listed Drug, Ditropan® XL (Alza), which has been listed in the FDA's "Orange Book" subsequent to our original submission. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

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JUL 28 2005
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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

July 28, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA NO. 76-644

"PATENT AMENDMENT"
PARAGRAPH IV CERTIFICATION
U.S. PATENT NO. 6,919,092

Dear Mr. Buehler:

Mylan previously filed its patent certification and exclusivity information for the above-referenced product. At the time of such filing, Mylan's certifications were correct. This current amendment is submitted to address a patent filing by the holder of the referenced drug, which was filed subsequent to Mylan's previous submissions.

Pursuant to Section 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act, Mylan certifies that in its opinion and to the best of its knowledge, U.S. Patent No. 6,919,092, which issued on July 19, 2005 is invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of Oxybutynin Chloride Extended-Release Tablets, 10mg for which this application is submitted.

Pursuant to Section 505(j)(2)(B) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.95(d), Mylan certifies it has, at the time of the filing of this amendment, given notice to the owner of the patent which is the subject of the certification, or its representatives, and also to the holder of the approved application for the listed drug claimed by said patent. Said notice complies with the requirements set forth in 21 CFR 314.95(c) with respect to the content of the notice.

Department—Fax Numbers
Accounting (304) 285-6403
Administration (304) 599-7284
Business Development (304) 598-5419
Corporate Services (304) 285-6482
Human Resources (304) 598-5406
Information Systems (304) 285-6404
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Quality Assurance (304) 598-5407
Quality Control (304) 598-5409
Regulatory Affairs (304) 285-6407
Research & Development (304) 285-6419
Sales & Marketing (304) 598-3232

Further, in accordance with 21 CFR 314.95(e), Mylan commits to amend this application to provide documentation that the notification sent to the patent owner and application holder has been received.

The patent certification set forth herein is made as an addition to the patent and exclusivity information set forth in Mylan's previous submissions. All patent and exclusivity information set forth in those submissions remains intact and this letter is merely an update to reflect Mylan's certification to the newly filed patent.

Sincerely,

Dawn J. Beto, Esq.
Associate General Counsel

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 19, 2005

MINOR AMENDMENT - REQUEST FOR FINAL ANDA APPROVAL
(CHEMISTRY AND ELECTRONIC LABELING INFORMATION ENCLOSED)

ORIG AMENDMENT
N 000
AM

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Request for Final ANDA Approval)

RECEIVED
AUG 2 2 2005
OGD/CDER

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on January 12, 2005, and to the patent litigation pertaining to this application which has not yet been resolved. A copy of the January 12, 2005 Tentative Approval letter has been provided in Attachment A for your reference. As the applicable receipt date of the paragraph IV patent certification notice by the patent owner and NDA holder was March 25, 2003, the 30-month period from the date of said receipt will expire on September 25, 2005. In accordance with the conditions outlined in the January 12, 2005 tentative approval letter and pursuant to 21 CFR 314.107(b)(3)(i)(A), Mylan hereby requests that final approval of ANDA 76-644 be granted upon expiration of the 30-month period. This request for final approval is based on the following application history:

1) ANDA 76-644 was submitted to the Agency on January 21, 2003 and considered acceptable for filing on January 22, 2003, as acknowledged in the Agency's letter dated March 10, 2003.

2) Mylan's Amendment dated May 27, 2003 provided documentation of receipt of the paragraph IV patent certification notice to the patent and NDA holders as required under section 505(j)(2)(B)(i) of the FD&C Act.

3) Expiration of the 30-month period provided for in section 505(j)(2)(B)(i) since the date of receipt of the 45-day notice required under section 505(j)(2)(B)(i) of the Act will occur on September 25, 2005.

As the patent litigation is currently ongoing and no court decision has yet been rendered, Mylan hereby requests that final approval of ANDA 76-644 be granted on the 30-month provision provided for in 505(j)(5)(B)(ii) of the Act.

As required by the January 12, 2005 Tentative Approval letter, this amendment also provides notification of the following changes to the conditions outlined in the chemistry, manufacturing and controls (CMC) of this application since the receipt date of Tentative Approval. The proposed production Master Batch Record for Oxybutynin Cloride Extended-release Tablets, 10mg has been revised to allow for the use of an alternate imprinter, a [redacted] (b) (4) imprinter manufactured by [redacted] (b) (4) for imprinting the finished drug product (refer to page 35 of the revised batch record provided in Attachment B).

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Corporate Services	(304) 598-5404	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

The currently registered production batch record provides for the use of [redacted] or [redacted] imprinters. Per the FDA's Guidance for Industry *SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral Dosage Forms, Manufacturing Equipment Addendum* (January 1999), the [redacted] imprinters are within the same class/subclass; therefore, the addition of the [redacted] printer is considered a minor change. The processing parameters sheets used during manufacturing [redacted] have also been revised to include minor changes which are fully described on the cover sheets preceding the revised processing parameters sheets provided in Attachment C.

With respect to labeling, our Final Printed Outsert labeling (code OXYB:R1; Revised July 2005) and Final Printed Bottle Labels are provided herein. Mylan's previously submitted draft outsert (OXYB:RX6) submitted on October 13, 2004 has been further revised in accordance with the most recent approved labeling for the Reference Listed Drug (RLD) which was posted on the Agency's website on July 14, 2004. A side-by-side comparison of Mylan's final printed outsert (code OXBY:R1; Revised July 2005) to the previously submitted draft outsert is provided. For the reviewer's convenience, a copy of the Reference Listed Drug (RLD) labeling from the FDA Web Post (Approved July 14, 2004) is also included. Please refer to the enclosed labeling Electronic Table of Contents provided in Attachment D for details.

In accordance with the Agency's Guidances *Providing Regulatory Submissions in Electronic Format – ANDAs* and *Providing Regulatory Submissions in Electronic Format – General Considerations*, we enclose a CD-Rom which contains electronic labeling for Oxybutynin Chloride Extended-release Tablets as described in the electronic Table of Contents provided in Attachment D. As a review aid, Mylan has also included Microsoft Word version of the proposed final printed labeling. To access these Word files, a bookmark is provided within the pdf version.

As required by 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

August 31, 2005

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review. In accordance with 21 CFR 314.95(e), this amendment provides documentation of receipt of the notice required by 21 CFR 314.95(a) and (b), as it pertains to the Paragraph IV patent certification contained in our Patent Amendment submitted on July 19, 2005 for Oxybutynin Chloride Extended-release Tablets, 10mg. Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

The owner of the patent and the holder of the application for the listed drug were served with the required notice. Proof of delivery by Registered Mail, Return Receipt evidences receipt by Alza Corporation on July 26, 2005. A copy of the documentation evidencing Mylan's service and receipt is enclosed.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers
Accounting (304) 285-6403
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Sales & Marketing (304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

NFI
Not sued w/in
45 days on -0
1/24/0

September 16, 2005

PATENT AMENDMENT

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which is currently under review, and to our certification to U.S. patent 6,919,092 contained in our Patent Amendment submitted on July 19, 2005. Reference is also made to our Patent Amendment submitted on August 31, 2005 which provided Documentation of Receipt of Notice.

Mylan has not received any notice that legal action was taken within the 45-day statutory period as identified in 21 CFR 314.95(f). Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Mr. Martin Shimer, Branch Chief
Regulatory Support Branch

RECEIVED
SEP 19 2005
OGD/DFS

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Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMENDMENT
N/AM

September 16, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Response to Agency Telephone Call Received September 16, 2005)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which received Tentative Approval on January 12, 2005 and to our Minor Amendment - Request for Final Approval submitted on August 19, 2005. Reference is also made to a telephone call received on September 16, 2005 from Dr. Mike Darj, Review Chemist, in which he requested that we submit (1) revised drug substance specifications in accordance with the current USP and (2) updated long term room temperature stability data for the drug product.

As requested by Dr. Darj, our drug substance specifications have been revised in accordance with the current USP and the compendial Assay and Related Compounds procedures have been adopted. The revised specifications, and compendial Assay and Related Compounds procedures with their associated method validation reports are provided in Attachments A, B and C, respectively. Updated room temperature stability data through 36 months for Oxybutynin Chloride Extended-release Tablets, Lot R1K0797, is provided in Attachment D.

As required by 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Dr. Mike Darj, Review Chemist
Division of Chemistry III, Team 4

RECEIVED
SEP 19 2005
OGD/CDER

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Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

ORIG AMEND
N/AM

September 21, 2005

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Response to Agency Telephone Call Received September 19, 2005)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which received Tentative Approval on January 12, 2005, our Minor Amendment - Request for Final Approval submitted on August 19, 2005, and our Telephone Amendment submitted on September 16, 2005. Reference is also made to a telephone call received on September 19, 2005 from Dr. Mike Darj, of your Office, in which he recommended that we submit revised drug substance specifications to (b) (4) to be consistent with those recently submitted by our supplier.

As requested by Dr. Darj, our drug substance specifications have been revised to (b) (4) to be consistent with our supplier. The revised drug substance specifications and revised (b) (4) procedure (b) (4) are provided in Attachments A and B, respectively.

As required by 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Dr. Mike Darj, Review Chemist
Division of Chemistry III, Team 4

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SEP 2 2 2005
OGD/CDER

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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 29, 2005

GENERAL CORRESPONDENCE
(PATENT INFORMATION ENCLOSED – NOTIFICATION OF DISTRICT COURT DECISION)

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(General Correspondence – Notification of District Court Decision)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005 and to our Minor Amendment - Request for Final Approval submitted on August 19, 2005. Reference is also made to our Patent Amendment submitted on May 27, 2003 in which we notified the Agency that Alza Corporation had commenced litigation against Mylan on May 2, 2003 with regard to the Paragraph IV certification submitted in this application pertaining to U.S. Patent No. 6,124,355.

In our August 19th amendment, we acknowledged that the patent litigation pertaining to this application had not yet been resolved. The purpose of this correspondence is to provide a copy of the September 27, 2005 decision from the U.S. District Court for the Northern District of West Virginia (Civil Action No. 1:03CV61). A copy of the district court decision is provided in Attachment A. As noted on page 57 of the attached decision, the court has concluded that Mylan's Oxybutynin Chloride Extended-release Tablets, 10mg does not infringe U.S. Patent No. 6,124,355 and the patent is invalid.

Based on this favorable court decision, there are no legal barriers which would preclude the Agency's ability to render final approval of this application. A similar correspondence, including a copy of the enclosed court decision, is also being submitted to Mylan's pending ANDA 76-702 for Oxybutynin Chloride Extended-release Tablets, 5mg.

This correspondence is submitted in duplicate. Should you require additional information or have any questions regarding this correspondence, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Department—Fax Numbers					
Accounting	(304) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Maintenance & Engineering	(304) 598-5411	Research & Development	(304) 285-6409
		Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 27, 2005

ORIG AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(CMC INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Response to Agency Telephone Call Received October 24, 2005)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005, our Minor Amendment - Request for Final Approval submitted on August 19, 2005, and our Telephone Amendments submitted on September 16, 2005 and September 19, 2005. Reference is also made to a telephone call received on October 24, 2005 from Dr. Mike Darj, of your Office, in which he recommended that we submit revised drug substance specifications to (b) (4) (b) (4).

As requested by Dr. Darj, our drug substance specifications have been revised to (b) (4) (b) (4) to be consistent with our supplier. The revised drug substance specifications and revised (b) (4) procedure (b) (4) are provided in Attachments A and B, respectively.

With respect to the release mechanism of our formulation, the following description is included in our product labeling under the subsection entitled "System Components and Performance:"

> Oxybutynin chloride extended-release tablets are formulated to deliver oxybutynin chloride at a controlled rate over approximately 24 hours. The dosage form is comprised of a hydrophilic cellulose polymer matrix tablet surrounded by an enteric coating system. The enteric coat is insoluble in the low pH environment of the stomach. As the tablet passes through the stomach and enters the higher pH environment of the small intestine, the enteric coating dissolves and/or erodes to expose the polymer matrix tablet which swells and releases drug at a controlled rate via diffusion and/or erosion.

A hard copy of our prescribing information is provided in Attachment C for the reviewer's reference.

Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6403	Label Control	(800) 848-0463	Quality Control	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Regulatory Affairs	(304) 285-6407
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Research & Development	(304) 285-6409
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Sales & Marketing	(304) 598-3232

As required by 21 CFR 314.96(b), we certify that a true copy of this amendment, as submitted to the Office of Generic Drugs, has been forwarded to the FDA's Baltimore District Office.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

Desk Copy: Dr. Mike Darj, Review Chemist
Division of Chemistry III, Team 4

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

Appeal still pending in Fed. Court. CA #06-1019

August 17, 2006

XP

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT
(PATENT INFORMATION ENCLOSED)

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Response to Agency Telephone Call Received August 17, 2006)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above which was granted Tentative Approval on January 12, 2005. Reference is also made to a telephone call received on August 17, 2006 from Mr. Robert West, Deputy Director, of your Office, in which he requested a summary of the litigation history regarding this application.

On May 2, 2003, Alza Corporation filed a complaint against Mylan Labs and Mylan Pharms in the Northern District of West Virginia alleging that Mylan's filing of an ANDA for Oxybutynin Chloride Extended-Release Tablets, 10mg (ANDA 76-644) constituted an act of infringement under 35 U.S.C. 271 of United States Patent No. 6,124,355. On June 26, 2003, Alza filed suit in the same court alleging that Mylan's filing of an ANDA for Oxybutynin Chloride Extended-Release Tablets, 5mg (ANDA 76-702) constituted an act of infringement under 35 U.S.C. 271 under the same patent. The two cases were consolidated and assigned to Judge Irene M. Keeley under the case no. 1:03CV61. The district court on September 27, 2005 ruled in favor of Mylan in holding that both Mylan's products did not infringe the asserted claims. On October 11, 2005, Alza appealed the district court decision and oral arguments took place before the Federal Circuit on June 6, 2006 (Case No. 06-1019). A decision by the Federal Circuit is pending.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned by telephone at (304) 599-2595, ext. 6551 or by facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

RECEIVED
AUG 18 2006
OGD / CDER

Desk Copy: Mr. Robert West, Deputy Director
Office of Generic Drugs

Department—Fax Numbers					
Accounting	(800) 285-6403	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Label Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 14, 2006

PATENT AMENDMENT

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

10/2/06
Notice of ruling by U.S. Court of Appeals to upheld decision by lower court in favor of Mylan + Impax re: '355 patent.

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Patent Information Enclosed)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on January 12, 2005. Reference is also made to a telephone call received on September 13, 2006 from Mr. Robert West, of your Office, regarding the current litigation status of our application.

On September 6, 2006, the U.S. Court of Appeals for the Federal Circuit held the patent-in-suit to be invalid (Case No. 06-1019). Provided in Attachment A is a Patent Amendment letter from our Legal Department which provides specifics regarding the enclosed information.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

cc: Mr. Robert West, Deputy Director (via facsimile)

RECEIVED
SEP 15 2006
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Department—Fax Numbers		Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Accounting	(304) 285-6408	Intake Control	(800) 848-0463	Quality Assurance	(304) 598-5407
Administration	(304) 599-7284	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Business Development	(304) 598-5419	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
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MYLAN PHARMACEUTICALS INC
781 Chestnut Ridge Road • P.O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

September 21, 2006

GENERAL CORRESPONDENCE

MC

Office of Generic Drugs, CDER, FDA
Gary J. Buehler, Director
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS, 10MG
ANDA 76-644
(Response to Agency Telephone Call Received September 20, 2006)

Dear Mr. Buehler:

Reference is made to the Abbreviated New Drug Application (ANDA) identified above, which received Tentative Approval on January 12, 2005. Reference is also made to a telephone call received on September 20, 2006 from Mr. Robert West, of your Office, regarding the issuance of a 'mandate' following the final decision of the U.S. Court of Appeals for the Federal Circuit (Case No. 06-1019).

Provided in Attachment A is correspondence from our Legal Department regarding the issuance of the 'mandate" and its potential impact on the triggering of Mylan's180 days of marketing exclusivity as a first generic.

This amendment is submitted in duplicate. Should you require additional information or have any questions regarding this amendment, please contact the undersigned at (304) 599-2595, ext. 6551 or via facsimile at (304) 285-6407.

Sincerely,

S. Wayne Talton

S. Wayne Talton
Vice President
Regulatory Affairs

SWT/dn

Enclosures

cc: Mr. Robert West, Deputy Director (via facsimile)

RECEIVED
SEP 22 2006
OGD / CDER

Department—Fax Numbers					
Accounting	(304) 285-6407	Information Systems	(304) 285-6404	Purchasing	(304) 598-5401
Administration	(304) 599-7284	Labeler Code	(800) 848-0463	Quality Assurance	(304) 598-5407
Business Development	(304) 598-5419	Legal Services	(304) 598-5408	Quality Control	(304) 598-5409
Corporate Services	(304) 285-6482	Maintenance & Engineering	(304) 598-5411	Regulatory Affairs	(304) 285-6407
Human Resources	(304) 598-5406	Medical Unit	(304) 598-5445	Research & Development	(304) 285-6419
		Product Development	(304) 285-6411	Sales & Marketing	(304) 598-3232

Skanchy, Jeanne

From: Grace, John F
Sent: Tuesday, September 12, 2006 10:24 AM
To: Birch, Postelle; Skanchy, Jeanne
Subject: RE: Labeling Sign-off for ANDA 76-644 and 76-702 (Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg)

I concur

From: Birch, Postelle
Sent: Monday, September 11, 2006 1:13 PM
To: Skanchy, Jeanne
Cc: Grace, John F
Subject: RE: Labeling Sign-off for ANDA 76-644 and 76-702 (Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg)

The approval summary for 76-644 signed on 9/12/05 and the approval summary for 76-702 signed on 12/12/05 by team leader John Grace are both still acceptable.

Postelle D. Birch-Smith, PharmD
LCDR, USPHS
Labeling Reviewer
Office of Generic Drugs
MPNI-Room 2329
Rockville, MD 20855
Phone: (301) 827-7347
Fax: (301) 827-7884

From: Skanchy, Jeanne
Sent: Wednesday, August 16, 2006 3:12 PM
To: Birch, Postelle; Grace, John F
Subject: Labeling Sign-off for ANDA 76-644 and 76-702 (Oxybutynin Chloride Extended-release Tablets, 5 mg and 10 mg)

Hi Postelle and John,

These applications have been sitting with Bob West waiting for Citizen Petition to be resolved. He has requested that I check with labeling to see if there are any changes. I have attached the approval letters and labeling summaries for these applications.

Thanks,
Jeanne

<< File: 76644.ap.doc >> << File: 76644.Lab AP Sum.pdf >>

<< File: 76702.ap.doc >> << File: 76702LabAPsum.pdf >>

Thanks,
Jeanne

West, Robert L

From: Skanchy, Jeanne
Sent: Wednesday, August 16, 2006 3:16 PM
To: West, Robert L
Cc: Ames, Timothy W
Subject: RE: ANDAS 76-644 AND 76-702 FOR MYLAN'S OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS

Hi Bob,

I just emailed Postelle and John for labeling concurrence. I will let you know if the labeling is still acceptable.

Thanks,
Jeanne

From: West, Robert L
Sent: Wednesday, August 16, 2006 2:36 PM
To: Skanchy, Jeanne
Cc: Ames, Timothy W
Subject: ANDAS 76-644 AND 76-702 FOR MYLAN'S OXYBUTYNIN CHLORIDE EXTENDED-RELEASE TABLETS

Jeanne:

These approval packages (Mike Darj) have been with me for a LONG time. Please check with the labeling reviewer to make sure that the labeling remains acceptable for approval. The most recent review is dated 12/21/05.

Thanks,

Bob

West, Robert L

From: Parise, Cecelia M
Sent: Wednesday, November 08, 2006 8:24 AM
To: West, Robert L
Subject: RE: Memo to the record

Bob,

You also need the Bio memo regarding the fed study for both the Mylan and the Impax applications. As the fed studies were evaluated using point estimates vs. CI.

Cec

From: West, Robert L
Sent: Wednesday, November 08, 2006 8:19 AM
To: Parise, Cecelia M
Cc: Downs, Patricia L
Subject: RE: Memo to the record

Cec:

At this time, we're only approving Mylan's ANDA 76-644 (10 mg) and 76-702 (5 mg). Mylan's ANDA 78-293 (15 mg) remains under review. We will also be approving IMPAX's ANDA 76-745 for 5 mg, 10 mg, and 15 mg.

Pat:

Please let me know when the enantiomer memo is signed and finalized. I'll place copies in the jackets noted above,

Bob

From: Parise, Cecelia M
Sent: Wednesday, November 08, 2006 7:54 AM
To: West, Robert L
Cc: Downs, Patricia L
Subject: FW: Memo to the record

Bob,

I have three Mylan ANDAs and one Impax ANDA listed.

Cec

From: Parise, Cecelia M
Sent: Wednesday, November 08, 2006 7:45 AM
To: Downs, Patricia L
Cc: Buehler, Gary J
Subject: Memo to the record

<< File: DRUP Consult_Citizens petition 11-3-06.pdf >> << File: enantiomermemo.doc >>

Pat,

Would you please finalize the memo to the record with the attachment from DRUP. It should be filed in the ANDA's.

CC. Marguerita Sims, ORP and Sonal Vaid OCC

Thanks,

Shimer, Martin

From: Shimer, Martin
Sent: Wednesday, September 14, 2005 2:23 PM
To: Park, Sarah Soojung; Parise, Cecelia M; West, Robert L
Cc: Rickman, William P; Shimer, Martin
Subject: Oxybutynin Exclusivity Analysis

Sarah,

Here is how the exclusivity seats play out for Oxybutynin ER Tablets 5, 10 and 15 mg.

For the 5 and 10 mg strengths:
Mylan holds the seat for '895, '754, '268, '355, '115 patents outright as the first applicant to file a PIV certification. Mylan and IMPAX both provided a PIV certification and notice on 7/19/2005 to the later listed '092 patent. Mylan will not be blocked by IMPAX on these strengths as at a minimum Mylan shares on the '092 patent. Therefore we can fully approve Mylan's 10 mg tablet upon expiration of the 30 month stay(for the '355 patent) which is 9/25/2005. Also we can fully approve Mylan's 5 mg tablet upon expiration of the 30 month stay(for the '355 patent) which is 11/28/2005.

For IMPAX's pending ANDAs for the 5 and 10 mg strengths we will need to await both the expiration of their 30 month stays(also sued on '355) and the expiration of Mylan's 180 day exclusivity.

For the 15 mg strength:
IMPAX is the only applicant for this strength so they get everything

Oxybutynin ER Tablet Exclusivi...

Mylan 76-644 Oxybutynin 10 mg

	PIV cert Date	Date Notice Sent	Date Notice Received
'008#	1/22/03(orig)		3/25/2003
'337#	1/22/03(orig)		3/25/2003
'668#	1/22/03 (orig)		3/25/2003
'895	1/22/03 (orig)		3/25/2003
'754	1/22/03 (orig)		3/25/2003
'268	1/22/03 (orig)		3/25/2003
'355	1/22/03 (orig)		3/25/2003
'115	1/22/03(orig)		5/25/2003
'092	7/19/05(amend)	7/19/2005	7/26/2005

* Mylan was sued on the '355 patent only. 30 month stay is set to expire on 9/25/2005.
# indicates patent that has expired

Mylan 76-702 Oxybutynin 5 mg

	PIV cert Date	Date Notice Sent	Date Notice Received
'008#	3/13/03(orig)		5/28/2003
'337#	3/13/03(orig)		5/28/2003
'668#	3/13/03 (orig)		5/28/2003
'895	3/13/03 (orig)		5/28/2003
'754	3/13/03 (orig)		5/28/2003
'268	3/13/03 (orig)		5/28/2003
'355	3/13/03 (orig)		5/28/2003
'115	3/13/03(orig)		5/28/2003
'092	7/19/05(amend)	7/19/2005	7/26/2005

*Mylan was sued on the '355 patent only. 30 month is set to expire on 11/28/2005
# indicates patent that has expired

IMPAX 76-745 Oxybutynin 15 mg

	PIV cert Date	Date Notice Sent	Date Notice Received
'008#	PIII		
'337#	PIII		
'668#	PIII		
'895	5/23/03 (orig)		7/29/2003
'754	5/23/03 (orig)		7/29/2003
'268	5/23/03 (orig)		7/29/2003
'355	5/23/03 (orig)		7/29/2003
'115	5/23/03(orig)		7/29/2003
'092	7/19/05(amend)	7/19/2005	7/20/2005

*IMPAX sued on the '355 patent only. 30 month is set to expire on 1/29/2006
# indicates patent that has expired

IMPAX 76-745 Oxybutynin 5 and 10 mg

	PIV cert Date	Date Notice Sent	Date Notice Received
'008#	PIII		
'337#	PIII		
'668#	PIII		
'895	8/19/2003(amend)	Not provided	8/25/2003
'754	8/19/2003(amend)	Not provided	8/25/2003
'268	8/19/2003(amend)	Not provided	8/25/2003
'355	8/19/2003(amend)	Not provided	8/25/2003
'115	8/19/2003(amend)	Not provided	8/25/2003
'092	7/19/05(amend)	7/19/2005	7/26/2005

*IMPAX sued on the '355 patent only. 30 month stay set to expire 2/25/2006
# indicates patent that has expired

MEMORANDUM

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

DATE: October 13, 2006

FROM: Barbara M. Davit, J.D., Ph.D.
Deputy Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Acceptance criteria for fed bioequivalence (BE) studies

TO: ANDA 76-644
ANDA 76-702

Mylan submitted two ANDAs for oxybutynin ER tablet products, ANDA 76-644 and 76-702. Mylan conducted both fed and fasting BE studies to demonstrate that its product was bioequivalent to Ditropan XL.

For Mylan's fasting BE studies submitted to ANDAs 76-644 and 76-702, the Office of Generic Drug (OGD) used the acceptance criteria that the 90% confidence intervals of the log transformed test to reference ratios for C_{max} and AUC (two parameters, AUC to the last measurable time-point [AUC_{0-t}] and AUC extrapolated to infinite time [$AUC_{0-\infty}$]) fall within the BE limits of 80-125% (0.8-1.25). OGD consistently applied this approach to data from in vivo fasting BE studies since the 1992 posting of the Guidance for Industry: *Statistical Procedures for Bioequivalence Studies Using a Standard Two-Treatment Crossover Design.*[1] OGD applied these criteria in its review of the in vivo fasting BE studies submitted to ANDAs 76-644 and 76-702.

For Mylan's fed BE studies submitted to ANDAs 76-644 and 76-702, OGD applied the acceptance criteria in place at the time those studies were initiated. These criteria were that the geometric mean test to reference ratios (point estimates) for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} should fall within the limits of 80 to 125% (0.8 to 1.25). (The 90% confidence intervals were not applied). The generic drug industry was aware that OGD used point estimate acceptance criteria when

[1] This guidance was replaced in 2000 by the Guidance for Industry: *Bioavailability and Bioequivalence Studies for Orally-Administered Drug Products – General Considerations*. Under the new guidance, the same approach is in effect for evaluating fasting BE studies.

evaluating data from in vivo fed BE studies. A number of drug-specific guidance documents for industry were published by OGD throughout the early 1990s; these guidances generally contained the following statement: "In general, a comparable food effect will be assumed provided the AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} mean values for the test product differ no more than 20% from the respective mean values obtained for the reference product in this study."[2] Accordingly, many sponsors designed studies to meet the point estimate acceptance criteria and therefore those studies tended to be smaller than studies designed to meet the 90% confidence interval BE limits. The drug-specific guidances containing the statements about acceptance criteria for fed BE studies were withdrawn by 2000.

Subsequently, in the early 2000s, FDA changed its thinking and concluded that in many cases[3] fed BE studies were as important in establishing BE as fasting BE studies. This change in thinking was reflected in the Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies*. The guidance was posted on January 31, 2003.[4] FDA made a decision that any fed BE studies initiated before January 31, 2003 would still be accepted based on point estimate criteria (the AUC and C_{max} geometric mean T/R ratios must fall between 80-125%) without having to fall within the 90% confidence interval. Any fed BE studies initiated after January 31, 2003 would be expected to meet 80-125% BE limits with respect to the 90% confidence intervals of AUC and C_{max} geometric mean T/R ratios. OGD has consistently applied this approach with respect to the 90% confidence interval in its review of ANDAs that include fed studies. As a general matter, this approach reflects that studies initiated prior to January 2003 include fewer subjects and therefore may not pass the confidence interval test (despite the fact they are otherwise bioequivalent). Rather than making ANDA applicants with such study designs repeat their studies, it is consistent with principle that no unnecessary human research be done to permit these studies to be accepted provided they are nonetheless bioequivalent. 21 CFR 320.25.

Both the AUC and C_{max} point estimates for Mylan's two fed studies, both of which were initiated prior to January 31, 2003, met our point estimate criteria in effect at that time. However, as indicated above, OGD did not expect the 90% confidence intervals to be calculated and to fall within the acceptance limits of 80 to 125%. Therefore, consistent with OGD's practice, OGD deemed the two studies acceptable.

Here are the C_{max} BE data and study initiation dates for these two ANDAs.

ANDA No.	Product	Fed BE study initiation date	C_{max} point estimate	C_{max} 90% confidence interval
76-644	10-mg ER tablet	Oct. 28, 2002	1.18	1.07-1.29
76-702	5-mg ER tablet	Dec. 14, 2002	1.21	1.09-1.35

[2] The limits of 0.8 to 1.20 for arithmetic means correspond to limits of 0.8 to 1.25 for geometric means.
[3] The CDER Guidance for Industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies* lists circumstances when OGD expects ANDA applicants to conduct a fed BE study for a proposed generic drug product.
[4] Although this guidance is dated December 2002, the notice of availability was not published in the *Federal Register* until January 31, 2003 (68 Fed. Reg. 5026 (January 31, 2003)).

The studies for Mylan's oxybutynin ER tablets passed the criteria that were in effect at the time the studies were initiated (90% CI for fasting studies and point-estimate for fed studies). OGD reasonably concludes that Mylan's fed studies likely do not meet the 90% confidence interval bioequivalence limits because the studies were statistically powered to meet point-estimate criteria,[5] and not because the products are not BE. As noted above, many sponsors before January 31, 2003 designed studies to meet the point estimate criteria and therefore those studies were often smaller than studies designed to meet the 90% confidence interval criteria. Specifically, Mylan included from 28-35 subjects in its two fed BE studies. This is fewer subjects than the number we would expect to be enrolled today (about 60 subjects), using confidence interval rather than point estimate acceptance criteria, and based on oxybutynin pharmacokinetic variability. In addition, we note that oxybutynin extended release tablets is not a narrow therapeutic index drug. There is a wide dosing range for which the drug can be considered safe and effective.[6] We reasonably conclude that there is an absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when Mylan's proposed drug compared to Ditropan XL is administered at the same dose under similar conditions. Consistent with the principle that no unnecessary human research be done, OGD does not believe it is necessary for Mylan to conduct the fed BE studies again. Mylan's fasted BE studies and fed studies (using only point estimate approach without using the 90% confidence intervals) demonstrate BE to Ditropan XL. OGD has no reason to believe that Mylan's product would not be bioequivalent to Ditropan XL.

[5] More subjects are necessary to meet the criterion that the 90% confidence interval of the geometric mean ratios fall within 80-125% than to meet the criterion that the geometric mean ratio or point estimate fall within 80-125%.
[6] The FDA-approved Ditropan XL package insert states that adult patients can be treated with doses ranging from 5 to 30 mg/day.

MEMORANDUM

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

DATE: November 9, 2006

FROM: Cecelia M. Parise
Regulatory Policy Advisor to the Director
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Robert L. West
Deputy Director
Office of Generic Drugs
Center for Drug Evaluation and Research

Robert L West 11/9/2006

TO: ANDAs for Oxybutynin Extended-release Tablets
76-644, Mylan Pharmaceuticals
76-702, Mylan Pharmaceuticals
78-293, Mylan Pharmaceuticals
76-745, Impax Pharmaceuticals

SUBJECT: Enantiomers

Please see the attached memo from the Division of Reproductive and Urologic Drug Products (DRUP). The memo states that there is insufficient evidence to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, and that the absorption of the enantiomers is linear. Therefore, the decision by the Division of Bioequivalence not to apply confidence interval criteria to the enantiomers in order to establish bioequivalence for Oxybutynin Extended-release Tablets for the same reasons outlined in the memo from DRUP still stands and remains correct.

Memorandum

To:	Marguerita Sims, J.D. Office of Regulatory Policy
Through:	Mark Hirsch, M.D. Acting Deputy Director, DRUP 11/3/06 George Benson, M.D. Medical Team Leader, DRUP 11/3/06
From:	Marcea Whitaker, M.D. Medical Officer, DRUP 11/2/06 Ortiz, Stephan, R.Ph., Ph.D. Clinical Pharmacologist, OCPB 11/2/06
Date:	October 31, 2006
Re:	**Ditropan XL** **Citizen's Petition Response** **Second Review**
Sponsor:	Ortho-McNeil

Background: A Citizen's Petition was filed on August 29, 2005, by Ortho-McNeil (Ortho-Urology) requesting that the Commissioner require the application of standard bioequivalence criteria to oxybutynin and its active metabolite desethyoxybutynin "to ensure that approved generic versions of Ditropan XL ER tablets are both bioequivalent and clinically equivalent to the innovator product." The Petition further requested that these bioequivalence criteria apply to all four enantiomers [(R)- and (S)- oxybutynin and (R)- and (S)- desethyloxybutynin] in both the fed and fasted states. Consultations regarding this Citizen's Petition were completed by both the Office of Generic Drugs and the Division of Reproductive and Urologic Products (DRUP consult sent to ORP on December 5, 2005).

The Office of Regulatory Policy has requested that DRUP provide clarification on several apparently contradictory statements contained in the Ditropan XL® label and in ORP's draft response to the Citizen's Petition. Specifically, the clarification relates to statements relating to the activity of the (R) isomer of oxybutynin in the Office of Generic Drugs consultation versus statements in the Ditropan XL label.

The OGD consultation from 2005 states: "...there are insufficient data to conclude that the primary efficacy and safety activity resides with the minor enantiomer. The sponsor cites an *in vitro* study by Noronha-Blob et al (1990) as demonstrating higher

anticholinergic activity for the R-enantiomer than the S-enantiomer in animal tissues. This study does not offer strong evidence that primary pharmacological activity (safety/efficacy) is determined by the minor enantiomer. First, this study was done in animal tissue and it is not clear how the results can be applied clinically. Second, the authors themselves expressed doubts about any pharmacological advantages offered by the R-oxybutynin enantiomer."

The Clinical Pharmacology Section of the Ditropan XL label states that:

> "Antimuscarinic activity resides predominately in the R-isomer."

The ORP requested that DRUP clarify this apparent contradiction.

Executive Summary and Comments:

The Division of Reproductive and Urologic Products reviewed the ORP draft response to the Citizen's Petition which concludes "that relevant scientific information does not support the conclusion that primary safety and effectiveness resides with the minor enantiomer (R-oxybutynin) when administered in humans." We also reviewed the Ditropan XL labeling that identifies the R-isomer as having the predominant antimuscarinic activity.

The Division's current comments address only the parent compound and its enantiomers (R- and S-oxybutynin), and not the enantiomers of the metabolite, desethyoxybutynin. The formal position of OGD appears to be that bioequivalence (BE) of the metabolite (and thus, the R- and S- enantiomers of the metabolite) is not required. Therefore, the relative potencies of the R- and S-enantiomers of the metabolite is no longer an issue. We remind ORP that the measurement and the bioequivalence of the metabolite, desethyloxybutynin, were previously addressed in the original consultations from DRUP and OGD.

In regard to the R- and S-enantiomers of the parent compound, oxybutynin, we offer the following three comments:

1. **The studies cited by the Petitioner to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, specifically, Naronha-Blob et al (1990), and Kachur et al (1988), are *in vitro* animal studies and not studies designed to demonstrate the clinical benefit of R-oxybutynin over S-oxybutynin in man.**
2. **Since it has not been clinically demonstrated that the major activity of Ditropan XL resides in the minor enantiomer (R-oxybutynin), the Division agrees with the Office of Generic Drugs that there should be no requirement for sponsors to demonstrate separate bioequivalence for the enantiomers of oxybutynin.**
3. **The statement in Ditropan® and Ditropan XL® labeling that "antimuscarinic activity resides predominately in the R-isomer" is based on statements pertaining to non-clinical information submitted in the original**

Ditropan XL NDA application (1998). The Division currently would recommend that this sentence be removed from the Clinical Pharmacology section of the Ditropan and Ditropan XL labels. Optimally, the sentence would be completely removed from labeling, although it may be possible to add qualifying statements clarifying the source of the information and its unknown clinical relevance. This statement can be modified, deleted, moved, or further addressed when the sponsor submits new labeling to comply with the physician's labeling rule (PLR).

In summary, the Division believes that primary safety and efficacy have not been adequately demonstrated to reside with the R-enantiomer of oxybutynin in humans despite the wording in current labeling.

Discussion:

Herein, we provide a more detailed discussion of the issue in support of the preceding Executive Summary and Final Comments.

Based upon our understanding of the FDA BA/BE Guidance, entitled "*Bioavailability and Bioequivalence Studies for Orally Administered Drug Products*", we believe that all four of the following criteria must be met in order to require separate application of the BE criteria to enantiomers of a racemic mixture:

1) The enantiomers exhibit different pharmacodynamic characteristics.
2) The enantiomers exhibit different pharmacokinetic characteristics.
3) Primary efficacy and safety activity resides with the minor enantiomer, and
4) Nonlinear absorption is present for at least one of the enantiomers.

The discrepancy which ORP wishes DRUP to address involves the third criterion, "Primary efficacy and safety activity resides with the minor enantiomer." For Ditropan and Ditropan XL, the minor parent enantiomer is (R)-oxybutynin. The sponsor argues, based upon a preclinical *in vitro* study in guinea pigs (Naronha-Blob et al, 1990), that the (R)-oxybutynin carries both primary efficacy and safety. ORP's draft response to the Citizen's Petition refutes this claim citing lack of human data and applicability. A problem arises because the Clinical Pharmacology section of both Ditropan and Ditropan XL labels states that "antimuscarinic activity resides predominately in the R-isomer." This sentence, with accompanying citation, was present in the sponsor's original proposed labeling for NDA 20-897 (Ditropan XL) in a submission dated November 25, 1997, in section *3.6 Nonclinical Pharmacology, Toxicology and Metabolism.* The Sponsor stated:

> "The predominant mechanism of urodynamic action and systemic toxicity is generally considered to be mediated through oxybutynin's anticholinergic activity (Yarker et al, 1995). An increase in cholinergic activity and the resulting loss of peripheral control has been suggested as the mechanism for idiopathic detrusor instability (Eckford & Keane, 1993), which may be alleviated by the

anticholinergic activity of oxybutynin (Yarker et al, 1995). The spasmolytic, calcium antagonism, or anesthetic properties of oxybutynin may also play a contributing role in its therapeutic efficacy. Oxybutynin exists in two enantiomeric forms, with most of the anticholinergic properties residing in the (R)–isomer (Yarker et al, 1995). The marketed immediate release oxybutynin products (Ditriopan® and various generics), and OROS® (oxybutynin chloride) are racemates."

Reviewer's comment: The Yarker et al (1995) article was reviewed. No reference to chirality and pharmacodynamic effect was found within the article, suggesting that this section of the sponsor's submission was not appropriately referenced. The cited reference does not support the sponsor's claim.

Additional relevant information was located in the archived reviews of the original Ditropan XL NDA. In summarizing the Sponsor's submission, the Pharmacology/Toxicology reviewer stated:

"In contrast to the anticholinergic activity of oxybutynin, which resides predominately in the R-isomer, its spasmolytic actions are not stereoselective and are 500 times weaker."

Reviewer's comments: 1) Despite this statement by the original Pharmacology/Toxicology reviewer, sufficient evidence was not submitted to support the statement that the R-isomer is responsible for the majority of the clinical anticholinergic activity. 2) Therefore, based on this lack of data to support this specific sentence in the labeling, modification of the Clinical Pharmacology section of the Ditropan and Ditropan XL labels would be appropriate.

In discussions with the DRUP Pharmacology/Toxicology review team, it is clear that the data which supported the above statement in labeling came from studies performed *in vitro* and in animals and not from *in vivo* human data.

Additional relevant information is found in the October 11, 2006, consultation from the Office of Generic Drugs to ORP, wherein OGD stated:

1) The "...current, relevant scientific information does not provide persuasive support for the assertion that primary safety and efficacy of the drug resides with the R-enantiomer of oxybutynin when administered to humans."
2) "Absent sufficient clinical testing for precise measurements of the drug's activity (including relative contributions of enantiomers) in humans, we do not think it is appropriate to rely on these animal studies to predict specific drug activity (e.g., relative contributions of enantiomers to safety and effectiveness) or correlation in humans."
3) "In sum, current, relevant scientific information does not provide persuasive support for the conclusion that the primary safety and efficacy of the drug reside with the R-enantiomer of oxybutynin."

Reviewer's comment: The DRUP review team agrees with the above statements made by OGD.

Conclusions:

1. The current comments address the parent compound, R- and S-oxybutynin, and not the metabolite, desethyoxybutynin. The formal position of OGD appears to be that bioequivalence (BE) of the metabolite (and thus, the R- and S- enantiomers of the metabolite) is not required. Therefore, the relative potencies of the R- and S-enantiomers of the metabolite is no longer an issue. We remind ORP that the issues of bioequivalence (BE) and measurement of the metabolite (and the R- and S- enantiomers of the metabolite) were previously addressed in the original consultations from DRUP and OGD.
2. The studies cited by the Petitioner to support the notion that R-oxybutynin is the enantiomer primarily responsible for efficacy, specifically, Naronha-Blob et al (1990), and Kachur et al (1988) are *in vitro* animal studies and not studies designed to demonstrate the benefit of R-oxybutynin over S-oxybutynin in man.
3. Since there is insufficient evidence that Ditropan XL's major activity has been clinically demonstrated to reside in the minor enantiomer (R-oxbutynin), we agree with the Office of Generic Drugs that there should be no requirement for sponsors to demonstrate separate bioequivalence for the enantiomers of oxybutynin.
4. The statement in Ditropan® and Ditropan XL® labeling that "antimuscarinic activity resides predominately in the R-isomer" is based on statements pertaining to non-clinical information submitted in the original Ditropan XL NDA application. We currently believe that this sentence should be removed from the Clinical Pharmacology section of the Ditropan and Ditropan XL labels, or at minimum, qualified so that the unknown clinical relevance of this nonclinical information is made clear.
5. Finally, even if human data were available which demonstrated that R-oxybutynin is predominately responsible for the anticholinergic activity, the fourth criterion necessary for requiring BE evaluation of enantiomers ("nonlinear absorption is present for at least one of the enantiomers") has not been met.

Reference:

Yarker, Y., Goa, K., & Fitton, A. (1995). Oxybutynin: A Review of its Pharmacodynamic and Pharmacokinetic Properties, and its Therapueutic Use in Detrusor Instability. Drug and Aging, 6 (3): 243-262.

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-644 Applicant Mylan Pharmaceuticals Inc.
Drug Oxybutynin Chloride Extended-release Tablets Strength(s) 10 mg

APPROVAL ☑ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 14 Sept 2005 Date 8/16/06 for
Initials MMS Initials AW

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = NDA# 20-897
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☑ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☑ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☑ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☑ No ☐
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: ~~Full~~ Please see e-mail & Holdes
Comments: Mylan prevailed in DC. Ct regarded to 1355 patent Elig Dir for Full Approval

2. Project Manager, Sarah Purk Team 4
Review Support Branch
Date 9/12/2005 Date
Initials SRP Initials

Original Rec'd date 1/22/2003
Date Acceptable for Filing 1/22/2003
Patent Certification (type) II, IV
Date Patent/Exclus.expires see attached
Citizens' Petition/Legal Case Yes ☒ No ☐
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒

EER Status Pending ☐ Acceptable ☑ OAI ☐
Date of EER Status 8/20/2003
Date of Office Bio Review 8/13/04 (AC)
Date of Labeling Approv. Sum 9/12/2005 12/12
Labeling Acceptable Email Rec'd Yes ☑ No ☐
Labeling Acceptable Email filed Yes ☑ No ☐
Date of Sterility Assur. App. N/A
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☑ No ☐

Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☒ No ☐
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☑
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date 1/12/2005
Previously reviewed and CGMP def. /NA Minor issued ☐ Date
Comments:
TA'ed 1/12/2005

3. David Read (PP IVs Only) Pre-MMA Language included ☑
OGD Regulatory Counsel, Post-MMA Language Included ☐
Comments: see review. OK. OTR 12/5/6
Date 9/16/05
Initials DTR

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments: cmc satisfactory.
Date 9/22/05
Initials

REVIEWER: **FINAL ACTION**

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
Refer to "sister" ANDA 76-702 (5mg strength).

6. Vacant RLD=Ditropan XL Extended-release tablets, 10mg
Deputy Dir., DLPS NDA 20-897 (002) Date_____
ALZA Corp Initials_____

7. Peter Rickman Date 9/23/05
Director, DLPS Initials
Para.IV Patent Cert: Yes ☑ No ☐; Pending Legal Action: Yes ☑ No ☐; Petition: Yes ☐ No ☐
Comments:
See Marty's Table & E-mail for patent info 30 month stay expired
'355 patent on 9/25/2005 Full AP after 9/25/05
OR Exclusivity NPP - carve-out w/ PCA Ext
Labeling acceptable 9/12/2005 per AP Summary
Office Lvel Bio acceptable 8/13/04 (Fastin is Fed studies) NO DSI inspec. needed
EER acceptable 8/20/2003

8. Robert L. West O/C for Full AP after 9/25/05
Deputy Director, OGD Date_____
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☒ No ☐; Petition: Yes ☒ No ☐ Initials_____
Comments: Acceptable EES dated 5/25/06 (Verified 8/16/06) No OAI audits ind
This ANDA was tentatively approved on 11/2/05 pending expiration of the 30-
month period on 9/25/05 for '355 patent. Refer to the administrative sign-off form
completed at that time. On 8/19/05 Mylan submitted a minor amendment to propos
minor PI updates and to request final approval after the 9/25/05 additional O/C appro
were submitted by Mylan on 9/16/05, 9/21/05 and 9/27/05 - PEL found acceptable for
approval 12/12/05 (verified 2/13/06) O/C found acceptable for approval 11/20/05.
On 9/25/05, Mylan announced that it prevailed in the '355
patent litigation at the district court level.

9. Gary Buehler Date_____
Director, OSD Initials_____
Comments: This ANDA is recommended for approval
First Generic Approval ☒ PD or Clinical for BE ☐ Special Scientific or Regulatory Issue ☐
EES data verified 11/9/06 (BW)

10. Project Manager, Team 12 - Jeanne
Review Support Branch Date 11/13/06
NA Date PETS checked for first generic drug (just prior to notification to firm) Initials JS
Applicant notification:
9:50 AM 11/13/06 Time notified of approval by phone 11/9/06 Time approval letter faxed
FDA Notification:
11/13/06 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
11/13/06 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

Approval Letter Faxed to Orange Book Staff @ 301-827-7337: Date/Time: ∅

Note: Mylan is eligible for 180-day generic drug exclusivity with respect to the '895, '954, '268, '355, and '115 patents. Mylan will share eligibility/1st exclusivity with Impax on the '002 patent.

File V:/division/dlps/approvrqu9.doc

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/s/

Patricia L. Downs
11/9/2006 10:09:10 AM
SECRETARY

Cecelia Parise
11/9/2006 10:16:36 AM
CSO

Robert L. West
11/9/2006 10:36:16 AM
CSO